Effects of interictal discharges on cognition and behaviour in children with well-controlled epilepsy

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Abstract

Objective: There is evidence that in patients with epilepsy interictal discharges can be accompanied by transitory cognitive impairment (TCI). However, it is not known whether interictal discharges and TCI impair day to day psychosocial functioning, and if so whether drug treatment to suppress discharges is effective in the absence of clinical seizures.

Aims of study: (1) Effect of lamotrigine on interictal discharges, behaviour and cognition in children with epilepsy. (2) Effect of interictal discharges on behaviour and cognition in children with epilepsy. (3) Effect of suppression of discharges behaviour in children with epilepsy.

Method: In a randomised, double-blind, placebo-controlled, cross-over study with lamotrigine ambulatory EEG, cognitive test battery and behavioural scores were measured in 61 patients at baseline, placebo and lamotrigine phase.

Results:

Interictal discharges are common in children with epilepsy even if seizures are well controlled. Lamotrigine reduced the duration of discharges per hour, but not the total number per hour in this group of patients. Lamotrigine had no significant negative or positive effect on cognitive performance in children with epilepsy. TCI was found in over 50% of patients with sufficient discharges for analysis. There was a significant correlation of side of discharges to the type of test (spatial or verbal), when correcting for dominant hemisphere. Interictal discharges were associated with impaired cognitive performance (working memory). During treatment with lamotrigine global rating of behaviour significantly improved in patients with a reduction in discharges rate, but not in patients with without a change in discharge rate. This was independent of randomization or presence of seizures.

Conclusion: Interictal discharges are common even in children with well-controlled epilepsy and associated with cognitive impairment, particularly affecting working memory. Our data suggest that suppressing interictal discharges can improve behaviour in children with behavioural problems and epilepsy.

Abstract 2

Table of contents 3

Acknowledgements 9

Own Contributions 11

List of tables 12

List of figures 14

List of abbreviations 16

Chapter 1: Introduction 17

1.1. Seizures and epilepsies 17

1.1.1. Classification of epileptic seizures and syndromes 17

1.1.2. Pathophysiology of seizure activity 18

1.2. Cognitive and psychosocial function in children with epilepsy 19

1.2.1. Cognitive impairment 21

1.2.1.1. Intellectual ability 21

1.2.1.2. Scholastic performance 21

1.2.2. Behavioural problems 22

1.2.3. Factors affecting cognition and behaviour 25

1.2.3.1. Aetiology 25

1.2.3.2. Age of onset 26

1.2.3.3. Seizure variables 27

1.2.3.4. Social factors 29

1.2.3.5. Antiepileptic drugs 29

1.2.3.6. EEG abnormalities 37

1.3. Electroencephalography 39

1.3.1. History 39

1.3.2. Origin of the EEG 41

1.3.3. Technology of EEG recording 42

1.3.4. Normal activity recorded in the EEG 44

1.3.5. Other types of EEG activity 47

1.3.6. Maturation of the EEG 47

1.3.7. The Abnormal EEG in epilepsy 48

1.3.7.1. Ictal discharges 49

1.3.7.2. Interictal discharges 51

1.4. Transitory Cognitive Impairment (TCI) 53

1.4.1. History and definition 53

1.4.2. Frequency of TCI in persons with epilepsy 54

1.4.3. Interaction between discharge and TCI 57

1.4.3.1. Effect of duration of discharge on TCI 57

1.4.3.2. Effect of type of discharge on TCI 58

1.4.3.3. Effect of lateralisation and localisation 59

1.4.3.4. Time of occurrence of discharge 60

1.4.4. Interaction between cognitive testing and TCI 61

1.4.4.1. Type of stimulus presentation and task continuity 61

1.4.4.2. Type of task 62

1.4.4.3. Complexity and difficulty of task 63

1.4.5. Interaction between cognitive test and discharge 64

1.4.5.1. Test situation 64

1.4.5.2. Duration of test 65

1.4.5.3. Difficulty of task 65

1.4.5.4. Localisation of discharges 66

1.4.6. TCI in benign partial epilepsy 66

1.4.7. Clinical relevance of TCI 68

1.4.8. Neuropsychological explanations 69

1.4.9. Practical implications 70

1.5. Lamotrigine 72

1.5.1. Introduction 72

1.5.2. Mode of action 72

1.5.3. Pharmacology 75

1.5.4. Adverse effects 76

1.5.5. Efficacy 78

1.5.6. Use in children 79

1.5.7. Effect on cognitive function and behaviour 82

Chapter 2: Aims of the study 88

Chapter 3: Methods 89

3.1. Methodological principles of testing neuropsychological functions 89

3.1.1. Intelligence test 89

3.1.2. Computerised neuropsychological test-battery 90

3.2. Methodological principles of behavioural measurements 96

3.2.1. Conner's parent and teacher rating scales 96

3.2.2. Statistical analysis 98

3.3. Methodological principles of TCI testing 99

3.3.1. Requirement of TCI tests 99

3.3.2. Type of cognitive test 100

3.3.3. Co-registration of EEG 101

3.3.4. Ngrams Test 102

3.3.5. Data analysis 111

3.4. Methodological principles of measuring SED 113

3.5. Study protocol 114

3.6. Patient recruitment 118

3.6.1. Inclusion criteria 118

3.6.2. Exclusion criteria 119

Chapter 4: Factors influencing the incidence of interictal discharges 120

4.1. Summary 120

4.2. Introduction 121

4.3. Methods 122

4.3.1. Patients 122

4.3.2. Procedure 112

4.3.3. Statistical analysis 123

4.4. Results 124

4.4.1. Clinical Findings 124

4.4.2. EEG findings 125

4.5. Discussion 128

Chapter 5: Effect of lamotrigine on interictal discharges 131

5.1. Summary 131

5.2. Introduction 132

5.3. Methods 133

5.3.1. Patients 133

5.3.2. Procedure 133

5.3.3. Efficacy and Safety Assessments 133
5.3.4. Statistical analysis 133
5.4. Results 134
5.4.1. Clinical findings 134
5.4.2. EEG findings 140
5.5. Discussion 146

Chapter 6: Effect of lamotrigine and interictal discharges on behaviour 150

6.1. Summary 150
6.2. Introduction 151
6.3. Methods 153
6.3.1. Patients 152
6.3.2. Procedure 152
6.3.3. Efficacy, Safety and Behaviour Assessments 152
6.3.4. Statistical analysis 152
6.3. Results 153
6.4. Discussion 158

Chapter 7: Effect of lamotrigine on behaviour 162

7.1. Summary 162
7.2. Introduction 163
7.3. Methods 165
7.3.1. Patients 165
7.3.2. Procedure 165
7.3.3. Neuropsychological test battery 165
7.3.4. Statistical analysis 166

7.4. Results 166

7.5. Discussion 177

Chapter 8: Effect of interictal discharges and TCI on cognition 182

8.1. Summary 182

8.2. Introduction 183

8.3. Methods 185

8.3.1. Patients 185

8.3.2. Procedure 185

8.3.3. Neuropsychological test battery 185

8.3.4. Statistical analysis 185

8.4. Results 187

8.4.1. Interictal discharges 188

8.4.2. TCI analysis 189

8.4.3. Relationship of ID, TCI and cognitive performance 194

8.5. Discussion 197

Chapter 9: Discussion 201

9.1. Summary of main findings 201

9.2. Considerations 202

9.3. Limitations of the study 206

9.4. Further Studies 208

Bibliography 210

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Own Contributions

Study design

The overall design of the study was arranged by my supervisor, Professor Colin Binnie. I was involved in some aspects of the study design such as the choice and design of the neuropsychological tests and clinical management. I obtained all relevant ethical committee approvals form King's College Hospital. Guy's Hospital and NCYPE, East Surrey.

Patient recruitment and clinical study

I have recruited all patients in this study myself. Recruitment involved travelling to distant hospitals in Maidstone, Canterbury and others. I was responsible for the day-to-day management and communication with children, parents, GPs and paediatritans. I was the sole point of contact for children and patients throughout the clinical part of the study (2 years). I performed all clinical and behavioural assessments and was involved with neuropsychological testing.

Data analysis

Together with Goigia Wilson I analysed most of the EEGs during neuropsychological testing (more than 300 hours worth of EEG recording). I supervised and assisted with the analysis of the ambulatory EEG recordings. I analysed all behavioural assessments and re-analysed all TCI test (some were initially analysed by S. Coleshill).

Statistical analysis and data interpretation

The analysis of all the data was originated by me with advice from Sabine Landau and R..., Institute of Psychiatry. All results were internally presented by myself and critically reviewed by Professor Colin Binnie and Professor Richard Robinson. I was responsible for the final presentation and interpretation of the data and determination of the results through writing up manuscripts and giving poster and platform presentation at national and international conferences.

List of tables

Table 1.1a Effects of old antiepileptic drugs on cognitive function and behaviour

Table 1.1b Effects of new antiepileptic drugs on cognitive function and behaviour

Table 1.2 Adverse events of lamotrigine reported in pooled paediatric and adult populations in open-label add-on studies

Table 1.3 Regimens for administration of lamotrigine

Table 3.1 Drug dosage regime

Table 3.2 Study Schedule

Table 4.1 Characteristics of patients

Table 4.2 Relationship of ID to age, gender, family history, neurological examination, IQ, behaviour, age of onset, type of epilepsy, antiepileptic drugs and seizures frequency

Table 4.3 Distribution of frequency of discharges (per hour) in respect to gender and type of epilepsy

Table 5.1 Baseline characteristics of patients

Table 5.2 Effect of lamotrigine on seizure frequency compared to placebo

Table 5.3 Most frequently reported drug related adverse events

Table 5.4 Interictal discharges at baseline and after each treatment phase

Table 6.1 Behavioural scores at baseline

Table 6.2a Observed changes in global score as well as parental behavioural subscale T-scores during placebo and lamotrigine phases

Table 6.2b Observed changes in teachers' behavioural subscale T-scores during placebo and lamotrigine phases

Table 6.3 Difference between groups and effect of covariates and within-subject factors

Table 7.1 Mean scores and reaction times of neuropsychological tests

Table 7.2 Effect of lamotrigine on cognitive function

Table 7.3 Bias in delayed recognition test (SMTS-16)

Table 7.4 Mean values of cognitive variables according to test session

Table 7.5 Mean differences of cognitive tests according to suppression of interictal discharges during active treatment.

Table 8.1 Occurrence of interictal discharges (ID) during ambulatory recording and cognitive testing

Table 8.2a TCI in Ngrams Corsi test.

Table 8.2b TCI in Ngrams Words test

Table 8.3 Summary of TCI results at different test sessions in patients with sufficient numbers of discharges during testing

Table 8.4 Association between TCI and lateralisation of epileptiform activity

Table 8.5 Mean values of cognitive test according to the three groups and One-way ANOVA

List of figures

Figure 1.1 Early EEG-registration by Berger, 1928

Figure 1.2 10-20 Electrode Placement System

Figure 1.3 Modified Maudsley system of electrode placement

Figure 1.4 Examples of bipolar montages: a) Neonatal montage. b) 'Double Banana' montage

Figure 1.5 Alpha rhythm

Figure 1.6 Beta activity

Figure 1.7 Theta activity

Figure 1.8 Posterior delta activity

Figure 1.9 Mu Rhythm

Figure 1.10 Lambda waves

Figure 1.11 Normal maturation of posterior dominant rhythm

Figure 1.12 Absence seizure with typical 3 per sec spike and wave activity

Figure 1.13 a) and b) Complex partial seizure in a 17 year old adolescent.

Figure 1.14 Generalised spike and wave without clinical correlate

Figure 1.15 Rolandic sharp wave

Figure 1.16 Schwab (1939): first TCI testing

Figure 1.17 Interaction between subclinical epileptiform discharges, neuropsychological test and cognitive function

Figure 1.18 Structure of lamotrigine

Figure 1.19 Mode of action

Figure 1.20 Efficacy of lamotrigine in children and adults

Figure 3.1 Continuous performance test

Figure 3.2 Serial Matching to Sample Tests SMTS-16 'Words'

Figure 3.3 CVST

Figure 3.4 Tiger test

Figure 3.5 EEG screen of a patient with benign epilepsy with centro-temporal spikes during TCI testing

Figure 3.6 Marking sheet for same patient

Figure 3.7 N-Grams-words

Figure 3.8 N-Grams-corsi

Figure 3.9 Study design, arrow indicates assessments
Figure 5.1 Trial profile
Figure 5.2a Distribution of frequency of discharges at baseline
Figure 5.2b Distribution of duration of discharges at baseline
Figure 5.3a Distribution of frequency of discharges at baseline after data values of 0.0 set to 0.01 and log transformation
Figure 5.3b Distribution of duration of discharges at baseline after data values of 0.0 set to 0.01 and log transformation
Figure 5.4 (a) Duration and (b) frequency of discharges in ambulatory EEG recordings at baseline and placebo. Data after values of 0.0 set to 0.001 and log transformation. Lines estimated 95% confidence regions
Figure 5.5 EEG findings at placebo and response to active treatment
Figure 7.1 Box plot for Tracer test
Figure 7.2 Box plot for FEPSY Recognition test: verbal and non-verbal
Figure 7.3 plot for STMS-16 delayed recognition test: faces and verbal scores
Figure 7.4 Box plot for CVST (score)
Figure 7.5 Box plot for CVST (reaction time)
Figure 7.6 Box plot for Tiger test
Figure 7.7 Box plot for Ngrams working memory spatial and words
Figure 7.8 Box plot for Ngrams working memory (reaction time)
Figure 8.1 Possible interaction between interictal discharges, brain pathology and cognitive impairment
Figure 8.2a Mean compound scores in Working memory test according to presence or absence of interictal dischargs and TCI
Figure 8.2b Mean reaction times in Working memory test according to presence or absence of interictal discharges and TCI
Figure 9.1 Interaction between interictal discharges, brain pathology and cognitive impairment

List of abbreviations

AED(s)	antiepileptic drug(s)
AMPA	d-amino-hydroxy-5-methyl-4-isoxazolepropionate
BECT	benign epilepsy of childhood with centro-temporal spikes
BL	baseline
CBZ	carbamazepine
CNS	central nervous system
CNZ	clonazepam
CSWS	Epilepsy with continuous spike and wave during slow wave sleep
EEG	Electroencephalography
ESES	Electrical status epilepticus during slow wave sleep
GABA	γ-Aminobutyric acid (GABA),
Hz	Herz
ID	interictal discharges
ILAE	International League against Epilepsy
IQ	Intelligence Quotient
LKS	Landau-Kleffner syndrome
LTG	lamotrigine
NMDA	*N*-methyl-*d*-aspartate
PB	phenobarbital
PHT	phenytoin
Plc	placebo
TCI	transitory cognitive impairment
VPA	sodium valproate

Chapter 1: Introduction

1.1. Seizures and epilepsies

1.1.1. Classification of epileptic seizures and syndromes

Epilepsy is generally defined as a condition characterised by the occurrence of recurrent epileptic seizures of cerebral origin. Epileptic seizures consist of a paroxysmal dysfunction of cerebral neurophysiological function and, in general, have a correlate on the electroencephalogram (EEG).

Epilepsy can be classified in several ways – by clinical events, aetiology, EEG changes, pathophysiology, anatomy, or age. In 1969 the International League against Epilepsy (ILAE) introduced a classification of seizure type, revised in 1981 (Commission on Classification and Terminology of the International League against Epilepsy, 1981), in which the EEG data are taken into account whereas aetiology, age, and anatomical side were ignored. In this scheme seizures are divided into three groups: generalised, partial and unclassifiable. Generalised seizures are further divided into absence (typical and atypical), myoclonic, clonic, tonic, tonic-clonic and atonic. Partial seizures, i.e. seizures beginning focally or locally, are divided into simple partial without impairment of consciousness and complex partial with alteration of consciousness. If seizures begin as partial seizures and then spread to become generalised, they are termed secondarily generalised.

An epilepsy syndrome may be defined as a disorder characterised by a cluster of signs and symptoms occurring together. The ILAE proposed a new scheme in 1989 which takes into account seizure type, EEG, prognostic, pathophysiological and aetiological data, the classification of the epilepsies and epilepsy syndromes and related seizure disorders (Commission on Classification and Terminology of the International League against Epilepsy, 1989). The main subdivision is into focal or localisation-related epilepsies and epilepsy syndromes on the one hand and

generalised epilepsies and epilepsy syndromes on the other. The two major dichotomies are into epilepsies characterised by seizures which are partial at onset and those which are primary generalised. The second dichotomy is between seizures that are idiopathic and those which are symptomatic. This usually devolves into those which have a genetic predisposition and those which are determined by a structural or lesional aetiology. Two new categories are added in this classification: cryptogenic (symptomatic aetiology is suspected but the aetiology is not known), and special syndromes. In contrast to adults it is usually easier and more practicable to classify seizure disorders in children according to syndromes rather than seizures. More recently the Task Force on Classification and Terminology of the ILAE has published a new proposal for a diagnostic scheme (Engel, 2001).

Conditions investigated in this thesis are idiopathic and symptomatic epilepsy syndromes of childhood. A population based epidemiologic study of epilepsy in school age children carried out in Italy found a prevalence of epileptics aged 5 to 14 years varied between 0.4% and 0.5%. The primary generalized epilepsies represent 30%, the epilepsies with rolandic spike foci 24%, the other types of partial epilepsy 42%, and the Lennox-Gastaut syndrome 3% (Cavazzuti 1980).

1.1.2. Pathophysiology of seizure activity

Seizures result from excessive synchronous electrical discharge (depolarisation) of the neurones in the brain due to an intercellular influx of sodium and calcium. Seizure activity begins when a number of neurones depolarise simultaneously. As initial depolarisation is caused by influx of calcium- and sodium-ions, blockade of ion channels stabilises the neuronal membrane and prevents depolarisation. A clinically apparent seizure occurs when the abnormal impulse spreads from its point of origin to adjacent and/or distant areas of the brain. γ-Aminobutyric acid (GABA), the major inhibitory neurotransmitter in the human brain, suppresses distribution of the impulse by opening neuronal chloride and potassium channels, thereby inducing membrane hyperpolarisation. A defect in the activity of GABA may therefore result in enhanced propagation of the epileptiform discharge.

Increased activity of excitatory neurotransmitters, such as glutamate and possibly aspartate, may also contribute to the spread of epileptic activity. Glutamate appears to be the main excitatory neurotransmitter involved in this process. Glutamate is active at several postsynaptic receptor sites, namely the *N*-methyl-*d*-aspartate (NMDA) receptor, the d-amino-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptor, the kinate receptor and the quisqualate receptor. After binding to the NMDA receptor, glutamate induces intermittent bursts of neuronal firing similar to those seen in an epileptic discharges. Antagonists of the NMDA receptor have been shown to be effective antiepileptics in animal models (Rogawski, 1992). Thus, it is at this receptor that glutamate is thought to exert its convulsive effects. Glutamate release depends on presynaptic membrane depolarisation produced by fast, transient, voltage-activated, inward sodium currents. These are followed by a brief period of fast inactivation. Slow inactivation gradually develops during sustained rapid firing that tends to terminate the discharge.

Infants and children are more prone to have seizures than adults. The immature brain appears to suffer from excessive depolarisation for a number of reasons. Factors which disturb energy production will cause failure of the adenosine triphosphate dependant Na-K pump (which maintains the cells equilibrium potential) and hence excessive depolarisation (Moshe, 1993). Hypoxemia, ischaemia and hypoglycaemia are common neonatal conditions which decrease energy production.

1.2. Cognitive and Psychosocial Function in Children with Epilepsy

Cognition can be defined as an individual's ability to acquire, retain, process and act upon information about and from the environment in an adaptive manner. This skill involves a wide range of mental processes including perception, memory, learning, attention, vigilance, understanding and interpretation. Behaviour, in the broadest sense encompasses all activities concerning autonomic responses and integrated reactions to dynamic situations, the experiencing and expressing of emotions and the

forming and maintaining of interpersonal relationships. Cognition and behaviour, therefore are the ways in which an individual interacts with the world and it's inhabitants. Cognition depends on many factors in the person's overall physical and mental state (e.g. pain, arousal, sensation and emotion).

The idea that epilepsy might be associated with loss of intellectual ability and emotional stability is not a new one. William Gowers (1885) said:

"The mental state of epileptics, as is well known, frequently presents deterioration ... In its slighter forms there is merely defective memory, especially for recent acquisition. In more severe degree there is greater imperfection of intellectual power, weakened capacity for attention and often defective moral control. Mischievous restlessness and irritability in childhood may develop to vicious and even criminal tendencies in adult life. Every grade of intellectual defect may be met with, down to actual imbecility."

More recently studies of quality of life have examined the difference between that in children with epilepsy and in other chronically ill children (Hoare, 1984; Austin et al., 1994, 1996, 1998). Austin et al. (1994) compared children with epilepsy and those with asthma, another chronic disease with unpredictable episodes, requiring medication and regular visits to a physician. Children with epilepsy showed a more compromised quality of life in psychological, social and educational domains, even though they developed their condition at a later age and were having fewer episodes. In contrast, children with asthma had a more compromised quality of life in the physical domain. This suggests that, in addition to dealing with a chronic disorder, other aspects of epilepsy are related to a poorer quality of life in psychosocial and cognitive domains.

It is an ongoing controversy as to whether the epilepsy causes cognitive and behavioural problems or whether epilepsy is to be viewed as a concomitant to the deterioration of cognitive function and behaviour. These explanations are not mutually exclusive. In this context, the definition of cognitive function will be the ability to deal meaningfully with information from the surrounding world, and the definition of behaviour will be the ability to interact with others.

1.2.1. Cognitive Impairment

1.2.1.1. Intellectual Ability

It is generally believed that people with epilepsy show scores in IQ tests between 5 to 10 points lower than healthy subjects. This, however, may reflect social factors and education rather than biological factors. The careful and often quoted epidemiological Isle of Wight study (Rutter et al., 1970) included 2193 10- and 11-year old children whose home was on the Island and was based on interviews and standardised rating scales completed by parents and teachers. Rutter and co-workers found an impairment of intelligence in those children whose seizures were associated with cerebral palsy or other brain disorders. Variability in distribution of IQ sub-tests was much greater and performance was worse on verbal tests than in normal children. A significantly higher proportion of children with epilepsy showed learning difficulties than would be expected in such a population.

In a large longitudinal study it was found that the mean IQ score of children with non-febrile seizures tested at 7 years was not significantly different from the mean score of their seizure-free siblings. Mental retardation was more common among children with seizures but the excess was accounted for by children who had neurological abnormalities before the first seizure (Ellenberg et al., 1986). Others found significantly lower mean IQ scores in a group of 50 children with idiopathic epilepsy and 25 of their non-epileptic siblings compared to 30 healthy controls (Singhi et al., 1992). The IQ scores of the children with epilepsy were also significantly lower than those of their siblings, suggesting that both the cause(s) of the epilepsy and the epilepsy itself have an effect.

1.2.1.2. Scholastic Performance

The majority of children with epilepsy are educated in mainstream schools. However, several surveys have consistently shown that problems of learning and behaviour are over-represented in such children (Ross et al., 1980). Harrison and Taylor (1976)

found that 90-95% of children with epilepsy were attending ordinary schools, whereas Verity and Ross (1985) in the National Child Development Study found that only 67% of 64 children with epilepsy attended ordinary schools at the age of 11 years, with only 58% attending at the age of 15 years. Attending mainstream school, however, does not imply that there are no scholastic problems. Holdsworth and Whitmore (1974) examined 117 children with epilepsy from mainstream schools, and found that 69% were considered by their teachers to be below average or falling seriously behind in their work. Twenty one percent had serious behavioural problems and 42% were markedly inattentive in class. Mellor et al. (1973) examined a large population of epileptic children attending mainstream schools in Scotland and compared their findings with those in healthy matched controls. Significantly more children with epilepsy performed poorly on a reasoning quotient, and 27% had behavioural problems, as rated by a questionnaire in comparison with 15% of controls ($p<0.05$).

More recently, using a questionnaire designed to look at educational problems and to be completed by teachers, Bennet-Levy and Stores (1984) showed that teachers perceive children with epilepsy as having poor concentration and mental processing, and as being less alert than their non-epileptic peers. Overall, they rate children with epilepsy as poor achievers, especially in mathematics.

Examining the academic achievements of 122 children with epilepsy, Seidenberg et al. (1986) noted that they achieved less than expected for their age and IQ. The greatest differences were in arithmetic, spelling, reading, comprehension and word recognition.

1.2.2. Behavioural Problems

Children with epilepsy are at a higher risk of developing behavioural problems and psychiatric disorders than their healthy peers. Early reports described multiple behavioural problems in children with epilepsy. Bradley reported mood fluctuations, hyperactivity, and irritability along with decreased attention span and selective

difficulty with mathematics (1951). Ounsted described distractibility, inattention, aggression, and mood labiality in children with epilepsy (1955). Pond noted neuroticism, aggression, and hyperactivity, and thought that neuroticism was relatively more associated with absence seizures and aggression with complex partial seizures of temporal lobe origin (1970).

Rutter's Isle of White study (1970) showed that psychiatric disorders occurred in 8% of the general population, in 16% of children with chronic medical disorders, 29% of children suffering from idiopathic epilepsy, and in 58% of epilepsy cases associated with structural cerebral abnormalities (Rutter et al., 1970). For recent reviews on psychiatric disorders in children with epilepsy see Gaitatzis et al. (2004) and Besag (2002).

Some children with epilepsy have specific attention problems (Holdsworth and Whitmore, 1974; Stores, 1973). Epileptic boys were significantly more inattentive than non-epileptic boys according to teachers and parents. In addition, they performed less well on tests of sustained attention and perceptual accuracy (Stores, 1978). Interestingly, no such differences were seen between two groups of girls with and without epilepsy. Others could not confirm such gender difference (Hoare and Kerley, 1991), but Austin et al. reported more problems in girls (1992).

Seizures in children have been associated with specific behavioural problems, with disruptive behaviours and mood disorder being found most commonly. There seems to be an association between epilepsy and autism, with seizures occurring in up to one-third of children with autism. Tuchman and Rapin (1997) have suggested that epilepsy and interictal discharges may be implicated in the pathophysiology of a minority of children with autism.

Weglage et al. (1997) assessed the behavioural status of 40 children with centro-temporal spikes with and without obvious seizures and compared them with 20 matched controls. The global score of children with discharges was significantly worse than controls, due to more problems in the subscales social problems, delinquent and compulsive behaviour.

Of the disruptive disorders, the association between attention-deficit/hyperactivity disorder (ADHD) and epilepsy has the best support from research data. Carlton-Ford

et al. reported impulsivity in 39% of children with a history of epilepsy versus 11% of controls (1995). Semrud-Clikeman and Wical (1999), using both structured interviews and a computerized continuous performance test, found that 33% of children with partial complex seizures had ADHD as defined by DSM-III-R criteria. Using either the Child or Adolescent Symptom Inventory, Dunn et al. (2003) noted symptoms of ADHD, combined type, in 11% and ADHD, predominantly inattentive type, in 24% of a sample of 175 children with chronic seizures.

As found in adults with epilepsy, there appears to be an association between depression and epilepsy in children and adolescents (Gaitatzis et al., 2004). Ettinger et al. (1998) reported elevated scores on the Child Depression Inventory in 26% of a sample of children 7–18 years of age with epilepsy. Dunn et al. (1999) found that 23% of a sample of adolescents with epilepsy had symptoms of depression. Oguz et al. (2002) noted more symptoms of depression in adolescents 12–18 years of age with epilepsy when compared with children 9–11 years of age with seizures or healthy controls. Children with complex partial seizures had elevated scores on the internalizing section of the CBCL, suggesting a risk for depression or anxiety (Schoenfeld et al., 1999).

Though the increased prevalence of behavioural problems has often been documented in children with chronic seizures, several studies have also shown an increased prevalence of behavioural problems in children with new-onset or recent-onset seizures. Aman et al. (1992) examined behaviour in a group of 112 children aged 6 to 12 years, with well-controlled seizures and normal IQ. They found significantly worse scores on all six subscales of the Child Behavior Checklist compared to a healthy control group. Subjects with partial seizures were rated as slightly more aggressive and antisocial than those with generalized seizures. Comparing behaviour in children with epilepsy and children with diabetes, Hoare (1984) found impairment in 48% of children with chronic seizures, 45% of children with recent-onset seizures, 17% of children with chronic diabetes, and 17% of children with recent-onset diabetes. Dunn et al. (1997) found that a fourth of the children with new-onset seizures had elevated scores on the Child Behavior Checklist, suggesting a risk for behavioural problems. Austin et al. (2001) found that

32% of the children with new-onset seizures had baseline behavioural scores in the clinical or at-risk range.

Medication side effects, such as the association between phenobarbital and increased hyperactivity (Vining et al., 1987), and psychosocial issues, such as the stigma of epilepsy, have been suggested as contributors to behavioural difficulties in children with epilepsy. However, a recent study documented behaviour problems prior to the time of first recognized seizures, suggesting that for some children epilepsy is a pervasive condition that includes both seizures and behaviour difficulties (Austin et al., 2001).

1.2.3. Factors affecting Cognition and Behaviour

These data confirm that children with epilepsy, even from non-selected groups, are more likely to fail academically and to show increased behavioural problems when compared not only with normal healthy children, but also with children having a different chronic disorder. Reasons for this are multifactorial and include underlying brain lesion, age of onset, seizure type and frequency, adverse social attitudes, antiepileptic drugs and EEG abnormalities (Kwan and Brodie, 2001). They need to be considered, both singly and in combination, in each individual child (Stores, 1990).

1.2.3.1. Aetiology

Several large studies have shown that patients with epilepsy and a history of structural lesions are more likely to develop intellectual impairment compared to patients with epilepsy but without such a history (Lennox 1942; Chevrie and Aicardi, 1972). However, these studies did not control for years of education. Bourgeois et al. (1983) found the mean IQ of children with idiopathic epilepsy to be 102.5 ± 16.1 and of children with symptomatic epilepsy to be 89.1 ± 29.6. Finally the Collaborative Perinatal Project (Ellenberg et al., 1986) found pre-existing neurological

abnormalities, including developmental delay, to be a significant predictor for poorer intellectual functioning in follow-up. There is no study comparing cognitive function in different idiopathic or cryptogenic epilepsy syndromes.

The type and anatomic location of the brain pathology have crucial impact on the type of cognitive deficit. Verbal memory deficit is more commonly associated with left-sided TLE and nonverbal or visual memory is typically affected in right temporal seizures (Kwan and Brodie, 2001; Meador, 2002). However, the extent of the neurocognitive dysfunction in focal epilepsies is usually more widespread.

Benign childhood epilepsy with centro-temporal spikes (also called Rolandic epilepsy) is regarded as an idiopathic epilepsy and was therefore believed not to be accompanied by any neurological or neuropsychological deficits. Several recent studies, however, have reported impaired visual-motor co-ordination (Heijbel and Bohman, 1975) and attention problems, particularly in children with right-sided discharges (Piccirilli et al., 1994). The only study including a matched control group found deficits in performance IQ, visual perception, motor skills and short term memory in children with rolandic epilepsy (Weglage et al., 1997). No significant differences could be found for simple finger-motor speed test or a linguistic test. Deficits in IQ were significantly correlated with frequency of EEG discharges, but not with seizure frequency, lateralisation of discharges or time since the Rolandic focus was diagnosed.

A number of rare epilepsy syndromes are linked with cognitive impairment, including Rasmussen' encephalitis and progressive myoclonus epilepsies such as Lafora body disease or MELAS. In these cases cognitive impairment clearly arises from impairment of brain function caused by the underlying disease, for example chronic encephalitis in a Rassmussen's patient.

1.2.3.2. Age of onset

Keith et al. (1955) found that the incidence of mental retardation (defined by various IQ measures) in children with seizures that began before the age of 6 months was

65%, from 6 months to 2 years 49%, from 2 to 4 years 34%, from 4 to 7 years 22% and from 7 to 15 years 12%. It is however, likely that the number of patients with severe epilepsies and consequent learning difficulties is over represented if the population is drawn from academic centres. Other studies have confirmed that the later in life patients experience their first seizure, the better their subsequent mental functioning (Rodin et al., 1968; Dikmen et al., 1975). Bourgeois et al. (1983) re-tested intelligence in children with epilepsy at yearly intervals and found that of children whose mean IQ decreased with time, seizures had begun at a significantly earlier age than those whose IQ did not decrease. Seizures may interfere with brain development and therefore may explain the poor prognosis for cognitive development in patients in whom the epilepsy starts early. Alternatively a severe underlying cerebral disturbance may cause both, an early onset and more obvious learning difficulties. Both processes may operate independently.

1.2.3.3. Seizure Variables

Evaluation of the effects of seizure frequency independent from effects of duration or severity of epilepsy may not be feasible. However, there is convincing evidence showing that higher frequency and duration of temporal lobe epilepsy are associated with more severe hippocampal atrophy and cognitive deficiency, possibly through secondary neuronal metabolic and structural deterioration (Dodrill, 1986). Seizure frequency has been found to influence information processing, alertness, short-term memory, and abstraction (Dodrill, 1986 and 2004). Generalized cognitive impairment with global decline in attention, memory, and general intelligence is more likely to be seen with increasing seizure frequency and epilepsy duration (Theodore et al., 1999). Seizure frequency has also been reported as among the most relevant determinants of poor quality of life scores in chronic epilepsy (Berto et al., 2002).

Development of hippocampal sclerosis and atrophy in patients with chronic temporal lobe epilepsy has been correlated with age at seizure onset, epilepsy duration, and a history of atypical and prolonged febrile seizures. Theodore et al. (1999) examined

MRIs of 35 patients with refractory temporal lobe epilepsy and found a significant correlation between the duration of temporal lobe epilepsy, history of febrile seizures, and severity of hippocampal sclerosis. However, the age at onset was not predictive of hippocampal sclerosis. Comparing patients with unilateral temporal lobe epilepsy of >30 years duration to those with 15–30 years duration, Jokeit and Ebner (1999) showed that psychometric intelligence of patients with longer duration of refractory temporal lobe epilepsy were more severely impaired.

Status epilepticus and prolonged or repetitive seizures may induce permanent neuronal injury and result in neuro-cognitive damage. However, this issue requires further evaluation as some authors have correlated the development of mental deterioration with repeated ''convulsive'' seizures or status epilepticus only (Dodrill, 1986; Duncan, 2002).

Pre- and post-ictal effects have also to be considered, but may be more difficult to detect and therefore for the family to accept. Nocturnal seizures are thought to have detrimental effects on language function and memory (Renier, 1987).

Patients experiencing more than one hundred generalised tonic-clonic seizures in their lifetime are more likely to suffer diminished intelligence than those experiencing occasional seizures. Since an early onset of epilepsy relates to a greater total number of seizures in a life time, this may be a confounding factor. Experiencing more than one type of seizure may impair mental functioning more than having only one seizure type (Dodrill 1992). It is believed that generalised tonic-clonic seizures and complex partial seizures have most effect on cognitive functioning (Dodrill, 1978; Seidenberg et al., 1981; Dodrill and Batzel, 1986). However, it can similarly be argued that a severe underlying cerebral disturbance may cause both more seizures and more obvious learning difficulties.

In children with idiopathic epilepsies, lower IQ scores are associated with a history of status epilepticus, the duration of the seizure disorder and the total number of seizures suffered (Singhi et al., 1992).

1.2.3.4. Social Factors

Adverse social attitudes play a major part, particularly the belief that a child with epilepsy is fundamentally incapable of the same levels of attainment as other children. As a consequence, expectations are set too low and the child is denied the usual encouragement to succeed. Equally to be avoided is setting too high expectations causeing low self-esteem. Such psychological factors have been relatively neglected in research on cognitive function in children with epilepsy, in favour of studies into biological influences (Whitman and Hermann, 1989). Furthermore, the restrictions imposed by parents and doctors to avoid seizure related injuries can impair the quality of life, although restrictions were often not adequately adapted to seizure-related risks and were therefore unnecessary (Carpay et al., 1997).

1.2.3.5. Antiepileptic Drugs

When focusing specifically on the cognitive aspects of antiepileptic drugs (AED) treatment it is important to realise that it can be difficult to isolate this issue from other aspects. AEDs can act on all of the processes if cognition (see section 1.2) and thereby indirectly affect the cognitive process. Even in objective neuropsychological tests, these other aspects will influence the measures. The use of neuropsychological testing, however, has been the major method of objectively measuring cognitive function related to the use of AEDs and approximately 100 studies on this issue have been published during the last 30 years. For recent reviews see Brunbech and Sabers (2002), Loring and Meador (2004) and Besag (2004). Despite this voluminous work, much uncertainty still exists with regard to the degree of cognitive effects of AEDs and whether there are significant differences in cognitive effects between the major AEDs. The reason for this uncertainty is a result of a number of methodological problems, which are dealt with in several reviews (Devinsky, 1995; Kwan and Brodie, 2001; Brunbech and Sabers, 2002; Loring and Meador, 2004).

These include: (a) no prospective data collection, (b) wider spontaneous cognitive fluctuations in patients with epilepsy, (c) no or inadequate control group, (d) testing patients during postictal phase, (e) sample size too small or trying to analyse more

factors than is warranted by the sample size, (f) testing two or more drugs simultaneously, (g) extrapolating data from normal volunteers to patients with epilepsy, (h) attributing observations to the AED by default, (i) comparing two drugs at doses that are not comparable, and (j) emphasising statistical significance over clinical relevance.

Bennet-Levy and Stores (1984) assessed the profile of cognitive function in 42 children with epilepsy attending mainstream schools comparing them with a group of matched controls. There were no significant differences in concentration, processing of information, alertness, confidence, and total attainment scores for reading, maths and spelling. However, patients receiving any AED showed lower scores for concentration, mental processing, alertness and total attainment scores than patients without medication. Various study designs have been used for the purpose of identifying and separating a possible drug effect and some of the studies in children will be discussed in the following.

Studies in healthy volunteers

The cognitive effects of gabapentin 2400 mg/day were compared with carbamazepine (mean dosage 731 mg/day) in a double-blind, randomised crossover study on 35 healthy volunteers (Meador et al., 1999). A neuropsychological test battery was administered at baseline and after a 5-week treatment period. Neuropsychological variables were attention/vigilance, dual task, cognitive/motor speed, memory, and executive functions. After a 1-month non-drug washout period the participants were retested. The procedure was duplicated after the second treatment and washout period. Gabapentin showed superiority compared with carbamazepine on eight out of 31 neuropsychological measures; however, compared to the non-drug period, gabapentin was favoured in one measure (verbal memory) but was inferior in four measures of speed and attention.

In a study on cognitive function in healthy volunteers, topiramate was compared to gabapentin and lamotrigine (Martin et al., 1999). Seventeen participants were divided into three groups and received on average topiramate 2.8 mg/kg, gabapentin 17 mg/kg or lamotrigine 3.5mg/kg per day. Cognitive tests and Profile of Mood

States (POMS) were administered at baseline, acutely (3 hours after medication), and after 2 and 4 weeks of receiving the drug. The cognitive tests used measured verbal fluency, verbal learning and retention, sustained attention, and psychomotor speed. Gabapentin and lamotrigine did not alter cognitive function significantly. Only the group treated with topiramate showed significant cognitive decline acutely and after 2 and 4 weeks. The study has been criticised for the small sample size, dosage size and administration, and the rather short test interval (Lhatoo et al., 2000).

However, data from healthy volunteers have to be treated with caution. In general the power of such studies is limited by small sample sizes and the drug-exposure period is limited. Thus, rare effects and effects due to longer term treatment can not be observed. Nevertheless, volunteer studies may provide information on the short term effects of an AED.

Comparisons between AEDs

Vining et al. (1987) compared cognitive and behavioural effects of PB and VPA in 21 children in a double-blind crossover fashion. While on sodium valproate, the patients scored significantly higher on full scale IQ, performance IQ, block design and Berkeley Paired Association Learning Test. While on phenobarbital, patients were rated significantly lower by their parents on three items for behaviour, and were also more hyperactive.

A potential pitfall when comparing neuropsychological effects of two AEDs is illustrated by the studies of Dodrill and Troupin. In their original crossover study of phenytoin and carbamazepine (Dodrill and Troupin, 1977), the performance of adult patients were significantly better for five variables while they were on carbamazepine. However, different blood levels were not taken into account. The study was reanalysed (Dodrill, 2004) and when patients with a baseline phenytoin level of ≥ 30 mg/L were eliminated, there were no significant differences. This reanalysis does demonstrate the shortcomings of the initial study, but is not in itself a valid demonstration of a lack of differences between the two drugs, since a high percentage of patients had to be excluded from the phenytoin arm and rendering the original randomisation invalid.

A multicentre study compared tiagabine with carbamazepine and phenytoin add-on to either carbamazepine or phenytoin monotherapy (Dodrill et al., 2000). The cognitive test battery measured verbal fluency, verbal learning and retention, visual learning. sustained attention, psychomotor speed and executive functions. 153 patients receiving carbamazepine monotherapy were randomised to add-on phenytoin (up to maximum 600 or 1000 mg/day) or tiagabine (up to maximum 80 mg/day), and 124 patients on phenytoin monotherapy were randomised to add-on carbamazepine (up to maximum 2000 mg/day) or tiagabine (up to maximum 80 mg/day). After a 16-week double-blind treatment period, no significant differences were seen with tiagabine compared with add-on carbamazepine or add-on phenytoin.

Studies in newly diagnosed patients

Studies in newly diagnosed patients have the advantage of being prospective, but the possible effect of seizure activity cannot be eliminated. In a placebo-controlled prospective study, 217 children with at least one febrile convulsion were randomised to either phenobarbital or placebo (Farwell et al., 1990). Compared with the placebo group, the mean IQ score of children randomised to phenobarbital was 8.4 points lower after 2 years of treatment, and 5.2 points lower after the medication had been discontinued. Stores et al. (1992) tested 63 schoolchildren with newly diagnosed epilepsy and 47 matched controls. Patents were randomly assigned to sodium valproate or carbamazepine and underwent testing before and 1, 3, 6, and 12 months after onset of treatment. Pre-treatment testing showed lower scores for visoumotor co-ordination and aspects of attention, as well as modest behavioural abnormalities among the children with epilepsy. During the early phases of treatment, mild cognitive and behavioural impairments were detected. Twelve months into treatment both drugs were effective in most cases at modest dosage without causing notable psychological effects. The authors concluded that the mild and temporary adverse cognitive effects seen earlier in treatment could have been the result of uncontrolled seizure discharge rather then drug related.

Comparison of high versus low doses or levels

Aman et al. (1990) tested 50 children on carbamazepine who had been seizure free for at least two months, once when the drug concentration was expected to be low and again at peak levels. During the peak concentration testing session, children showed lower scores for matching familiar figures and for auditory-visual integration, but higher scores for memory tasks, motor performance and in a continuous performance task. However, the concentration of carbamazepine levels in saliva did not correlate with any of variables measured.

Comparison of an AED versus placebo as add-on drug

This design is usually used for new AEDs in patients with drug resistant epilepsy. This design has several disadvantages: (1) patients are on two or three AEDs already and accumulative effects of the different drugs can not be differentiated; (2) effect of on-going seizure activity cannot be eliminated; (3) patients often have pre-existing learning difficulties and behavioural problems. However, for ethical reasons this design has to be used for II and early phase III studies and occasionally cognitive testing has been included in such studies. The addition of tiagabine could not be shown to cause clinically important changes in terms of cognition or quality of life effects in studies in adults (Kalviainen et al., 1996; Dodrill et al., 1997). For studies on lamotrigine see chapter 1.4.7.

Drug	Impairment of cognitive functioning	Behavioural disturbances	Author
CBZ	None		Gallassi et al., 1986
	No significant change		Aman et al., 1990
	No clear effect	No clear effect	Stores et al., 1992
	Impairment of memory in normal volunteers		Meador et al., 2001
PB		Hyperactivity	Ingram, 1986
	Impairment of short term memory		MacLeod et al., 1978
	Lower IQ scores compared to VPA		Vining et al., 1987
	persisting lower IQ in children with FC		Farwell et al., 1990
PHT	Reading skills impaired	Attentiveness	Stores, 1978
	Impairment at high serum levels		Nolte et al., 1980
	Disturbance of visuo-motor performance & IQ		Gallassi et al., 1987
	Impairment of memory in normal volunteers		Meador et al., 1993
VPA	Disturbance of visuo-motor performance, attention		Gallassi et al., 1990
	No clear effect	No clear effect	Stores et al., 1992
CNZ		Associated with behavioural disturbances	Browne, 1976

Table 1.1a: The effects of old antiepileptic drugs on cognitive function and behaviour

Drug	Impairment of cognitive functioning	Author
Oxcarbazepine	No significant difference compared to PHT	Äikiä et al., 1992
	No significant difference compared to PHT, PB, VPA, CPZ	Sabers et al., 1995
Topiramate	worsening on 1 variable (short term memory)	Aldenkamp et al., 2000
	deterioration in attention, vigilance and word naming	Meador et al., 1997
Tiagabine	no significant difference compared to PHT or CBZ	Dodrill et al., 2000
Gabapentin	significantly better performance compared to CBZ	Meador et al., 1999
	No change in psychomotor and memory tests	Leach et al., 1997
Levetiracetam	Small improvements in tapping rate, selective reaction time, and memory, but no control group	Neyens et al., 1995
Vigabatrin	improved on memory, and flexibility of mental processing compared to CBZ	Kälviäinen et al., 1995
	Impaired Digit Cancellation Test with increasing dose	Dodrill et al., 1995

Table 1.1b: The effects of new antiepileptic drugs on cognitive function and behaviour (for lamotrigine, see Chapter 1.4). CBZ: carbamazepine, PB: phenobarbital, PHT: phenytoin, VPA: sodium valproate, CNZ: clonazepam.

Withdrawal studies

Assessing cognitive and behavioural effects of AEDs by testing seizure-free subjects before and after discontinuation eliminates many confounding factors, in particular the effect of on-going seizure activity. A possible shortcoming of such a design is that it may not unmask potential chronic cumulative cognitive effects that are not or only slowly reversible. Also, control groups are essential to assess a possible learning effect. Gallassi et al. (1986, 1987, 1990) used a withdrawal design to study the effects of phenobarbital, carbamazepine, phenytoin and sodium valproate. A group of 16 adolescents and young adults, seizure-free on either phenobarbital or carbamazepine monotherapy were tested before and after discontinuation of the medication (Gallassi et al., 1986). Before discontinuation, patients on carbamazepine performed better than those on phenobarbital on one measure only (spatial span). One year after discontinuation, patients withdrawn from phenobarbital had improved on this same measure, patients withdrawn from carbamazepine had a shorter simple reaction time, and there were no differences between the groups. In a similar study of 10 adults discontinued from phenytoin monotherapy, patents performed worse than controls on three measures before the drug was stopped. No differences between patients and controls were detected 1 year after discontinuation, suggesting a reversible drug effect (Gallassi et al., 1987). Similarly, 20 seizure-free adults performed worse than controls on three measures before discontinuation of sodium valproate monotherapy (Gallassi et al., 1990), and these deficits were completely reversible within 1 year. In the so called Holmfried study 83 children with epilepsy who had been seizure free for at least one year, and 83 matched controls were tested before and after drug withdrawal (monotherapy with either carbamazepine, phenytoin or sodium valproate). Significant improvement was found in only one of the 12 cognitive tests, namely, psychomotor speed, suggesting that the impact of AED treatment on higher-order cognitive function is rather limited (Aldencamp et al., 1993; Tonnby et al., 1994). Another explanation would be that impairment of cognition and behaviour during a time of learning and information acquisition has long lasting impact, which my or may not diminish with time.

There is now considerable evidence that in adults polytherapy has a severe impact on cognitive function and can cause multiple types of cognitive impairment and

behavioural and psychiatric disturbances (Thompson and Trimble, 1982). Two drugs that individually have relatively mild cognitive effects may induce serious cognitive impairment when used together, possibly because of potentiation of tolerability problems (Trimble 1987). Duncan et al. (1990) studied the effect of discontinuation of sodium valproate, phenytoin or carbamazepine in 58 patients with active epilepsy treated with multiple AEDs and 25 controls. Simple motor skills became faster on discontinuation of phenytoin, carbamazepine, and sodium valproate. Attention and concentration improved on discontinuation of phenytoin. However, the position in children on polytherapy remains unclear.

Table 1 summarises the findings from some studies that examined the effects of certain antiepileptic drugs on cognition and behaviour.

1.2.3.6. EEG Abnormalities

The occurrence of subclinical epileptiform discharges in some patients with epilepsy has been correlated with poor cognitive functioning. Dodrill and Wilkus (1976) looked at cognitive functioning in adults with epilepsy. They compared those whose EEG showed subclinical epileptiform discharges with patients in whom discharges were absent, and found that lower intelligence scores were significantly associated with the presence of discharges, especially in patients in whom discharges were generalised rather than focal and occurred at an average rate of more than one per minute.

Continuous epileptic activity without motor components lasting for hours, days. or even weeks is often referred to as "non-convulsive status epilepticus". It may have a rather dramatic presentation as "pseudo-dementia" but often the changes are more subtle (Stores, 1986). Unfortunately, there has been little systematic research of the effects of such prolonged discharges on mental function. Stores et al. (1978) demonstrated significantly more behavioural disturbances in boys with left temporal discharges than in boys with epilepsy but without inter-ictal discharges. However, the difference between right and left sided discharges has not been confirmed by others.

Electrical status epilepticus during slow wave sleep (ESES) is an EEG phenomenon, describing the occurrence of epileptiform discharges during no less than 85% of non-rapid eye movement (non-REM) sleep of continuous, bilateral diffuse slow spike and wave activity, which abates during REM periods. It occurs in the following four epileptic syndromes: Epilepsy with continuous spike and wave during slow wave sleep (CSWS), Landau Kleffner syndrome (LKS), anterior opercula syndrome and some cases of benign partial epilepsy with centro-temporal spikes. CSWS is characterised by intellectual disturbance and behavioural problems in a previous normal child with age of onset between 3-9 years (Patry et al., 1971; Tassinari et al., 1985). LKS is characterized by language regression in the form of a verbal auditory agnosia in a previous normal child usually 3–9 years old. In both syndromes seizures occur in around two-thirds of children only and usually cease during adolescence. They may be of various types, often including generalised tonic-clonic seizures, absences and simple motor seizures. The neuropsychological importance of ESES lies in its association with concurrent global intellectual deterioration, which persists in some after ESES has abated (Robinson et al., 2001). It has been postulated that the long lasting persistence of spike wave during sleep is responsible for mental impairment and psychiatric disturbances. The aetiology of LKS is still unclear but it is likely that it has more than one. It has been suggested that at least in some patients the pathophysiology of the nocturnal discharges is the same as in benign partial epilepsy (see later) and that benign childhood epilepsy with centro-temporal spikes, ESES and LKS are not specific entities but in fact represent part of a spectrum disorder (Deonna, 1991; Jayakar and Seshia, 1991; Galanopoulou et al., 2000; Doose et al., 2000).

In addition to the possibility that seizures during sleep may themselves harm cognitive function, the quality of sleep may also be relevant. Evidence is accumulating that sleep fragmentation, i.e. repeated brief interruptions in the continuity of sleep, so-called micro-arousals, may be caused by epileptiform discharges and associated with impaired performance and other behavioural changes during the day (Levine et al., 1987).

Some studies have found no relationship between an abnormal EEG and behavioural disturbances (Hartlage et al., 1972; Mellor et al., 1974). However, in other

investigations, a temporal lobe focus has been found to be associated with disturbed behaviour (Stores 1978; Hoare 1984; Whitman et al., 1982) and with aggressive behaviour (Bagley, 1973) and dependency (Stores and Piran 1978).

There is an ongoing discussion as to whether the discharges may cause the cognitive dysfunction or whether both discharges and cognitive dysfunction are caused by the underlying pathology. These mechanisms are not mutually exclusive.

1.3. Electroencephalography

1.3.1. History

The discovery of the electroencephalogram was hailed by the following sentence in a short report published in the British Medical Journal on the electric currents of the brain by Richard Caton, an electrophysiologist in Liverpool, in August 1875. 'Feeble currents of varying direction pass through the multiplier when the electrodes are placed on two points of the external surface, or one on the surface of the skull'. Fifteen years later, Beck working in Krakow, Poland, explored the electrical activity of the brain in much greater detail and made great contributions to the techniques of localisation of sensory functions in the brain as well as to knowledge of the electroencephalogram. Many other scientists were also experimenting on the electrical activity of the brain at the same time but unknown to each other, most notably Danilevsky who described electrographic potentials in his doctoral thesis in 1876. Cybulski who was Beck's teacher and friend also contributed greatly to the investigation of the early electroencephalogram. In 1914 he published recordings of the spontaneous electrical activity of the cortex of the dog and monkey and demonstrated also the induction of an epileptic seizure in the dog. Meanwhile in Russia the subject of spontaneous oscillations in the brain were being explored by Kaufmann in St Petersburg and he was the first to demonstrate that an epileptic attack was accompanied by abnormal discharges. Another Russian scientist, Neminsky became interested in the electrical activity of the brain and in 1912

published the first photographs of the electroencephalogram - also unknown to Cybulski who published his photographs in 1914. Neminsky was the first to publish observations on the frequency of the activity in the EEG. He reported the oscillations from dogs to be 12-14 per second and those from the surface of the brain and dura as 12-20 per second but up to approximately 35 per second. He also found that in asphyxia these oscillations slowed to 4-7 per second.

Hans Berger, a German psychiatrist, using a string-galvanometer was the first to record the electroencephalogram in man in 1924. Only after developing a machine with a higher sensitivity, the coil-galvanometer in 1926 constructed by Siemens, could he convince himself that what he was measuring was actual brain electrical activity (Figure 1.1).

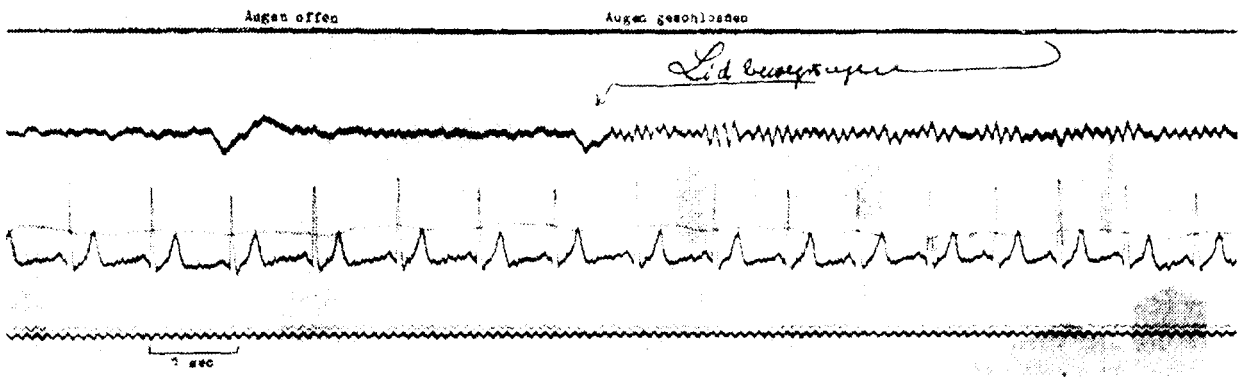


Figure 1.1: Early EEG-registration by Berger, 1928, one year before his first publication. Arrow annotates 'Augen geschlossen, Lid bewegungen' (eyes closed, lid movement) and correlates with the onset of α rhythm.

Five years after his discovery and following further experiments he published his findings in the German journal "Archiv fur Psychatrie" (Berger, 1929). Later he described alpha and beta activity in the physiological and pathological state and even recorded absence attacks with regular rhythmic high-voltage slow waves at a frequency of 3 per second. However he failed to demonstrate the associated spike and felt that what he had recorded was an artefact. The validity of his pioneering work and its value in diagnosing and treating epilepsy was shortly afterwards confirmed in Great Britain by Adrian and Matthews (1934) and in the United States by Gibbs,

Davis and Lennox (1935). The EEG rapidly gained value in other neurological conditions also, e.g. Gray Walter in 1936 described focal slow waves over brain tumours and until relatively recently, when CT and MRI became widely accessible, the EEG was the only non-invasive method for diagnosing intracranial mass lesions.

1.3.2. Origin of the EEG

The electroencephalogram (EEG) records potential differences of the order of microvolts (μV) between pairs of electrodes, measured continuously over time and displayed as a function of amplitude and frequency. EEG activity recorded from the scalp is of cortical origin, being derived from the post-synaptic potentials of the cortical pyramidal neurones. The depolarisation of cortical neurones may originate from elsewhere, e.g. the thalamus. It is a measure of the extracellular current flow associated with the summed activity of many (hundreds of thousands) individual neurones and postsynaptic potentials.

An excitatory post synaptic potential (EPSP) is a transient partial reduction in the negative membrane potential which is usually due to an increased local permeability to sodium and other cations. It is caused by presynaptic release of the excitatory neurotransmitter glutamate. An inhibitory post synaptic potential (IPSP) is a transient increase in the negative membrane potential usually the result of a local increase of permeability to potassium or chloride ions caused by presynaptic release of the inhibitory neurotransmitter GABA. Tonic activity in afferent fibres results in a long lasting EPSP with small fluctuations during which the EEG shows only a reduction in amplitude.

The dendrites of the pyramidal neurones guide the flow of currents generated by post-synaptic potentials at either the cell body in the deep layers of the cortex, or at the dendrites in the more superficial layers, through the entire thickness of the cortex. These neurones are closely packed and orientated parallel to one another, facilitating spatial summation of the currents generated by each neurone.

The factors that determine whether a cortical potential is recorded over the scalp include its voltage, the extent to which the generator cells are discharging

synchronously, the area of cortex involved and the orientation of neurones in respect to the surface. In bipolar recording, the net potential is proportional to the algebraic difference between the solid angles subtended by the generator surface at each individual electrode position. Radial dipoles from the gyri appear in the EEG, whereas tangential dipoles from the sulci do not, but may be recorded by magnetoncephalography.

The cortical activity has a regular rhythmicity that seems to depend on the functional integrity of subcortical mechanisms. The thalamus is believed to serve as a pacemaker of certain cortical rhythms that are recorded in the EEG such as sleep spindles. Postsynaptic inhibitory potentials synchronise the activity of the thalamic cells, thereby leading to the generation of a series of excitatory waves and governing the interval between successive waves (Andersen and Andersson 1975).

1.3.3. Technology of EEG recording

The EEG activity is measured with metal electrodes that are fixed to the scalp using an adhesive conductive paste and connected to a recording apparatus. Modern EEG recording machines are digital and the analog EEG signal recorded by electrodes is digitised by analog to digital converters and then displayed on screen. As different regions of the head generate different types of activity, electrodes have to be applied in a systematic fashion so that each area of the brain is studied. The need for a general electrode placement format led the International Federation of Societies for Electroencephalography and Clinical Neurophysiology to recommend a specific system of electrode placement for use in all laboratories under standard conditions. This is referred to as the 10-20 system of electrode placement (Fig. 1.2). Specific measurements from bony landmarks (nasion, inion and left and right pre-auricular points) are used to determine the placement of electrodes. The term 10-20 is used because electrodes are placed at points 10 % and 20% along lines between these bony landmarks. The standard numbering system places even-numbered electrodes on the right, and odd-numbered electrodes on the left with a letter designating the

anatomical area. Midline electrodes are designated with the letter 'z'. However this system has been criticised because of inadequate temporal lobe coverage.

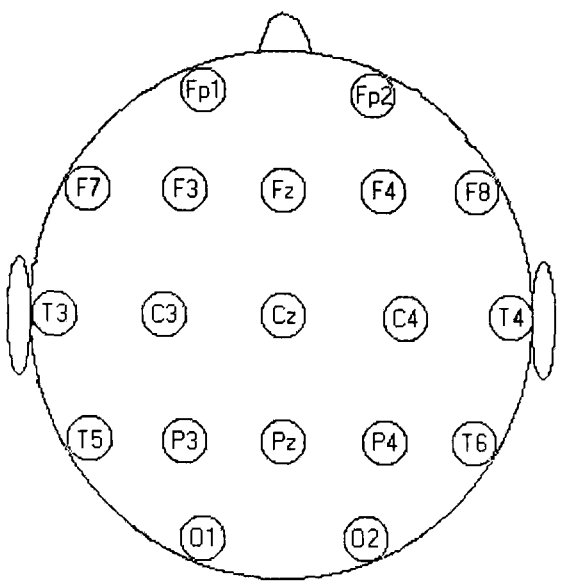


Figure 1.2: 10-20 Electrode Placement System.

Another system exists called the Modified Maudsley system of electrode placement, which provides more information on temporal lobe activity (Fig. 1.3) and which adapts itself better to abnormalities in cranial morphology (Binnie et al., 1982).

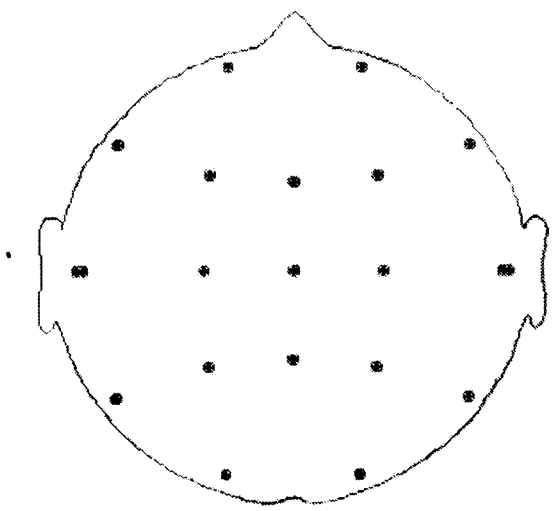


Figure 1.3: Modified Maudsley system of electrode placement

EEG activity can be displayed is dependent using different montages. A montage is a pattern of the electrode arrangements used for EEG display. They are generally selected so that recordings are made from rows of equidistant electrodes running

from the front to the back of the head or transversely across it. Examples of montages are illustrated on Figure 1.4. Recording arrangements can be varied so that the potential difference is measured between pairs of scalp electrodes (bipolar) or between individual electrodes and a common reference point. In the latter arrangement the reference site can be either a relatively inactive site (such as linked ears) or a point connected to all the electrodes in use so that it reflects the average of the potentials at these electrodes. Most modern digital EEG machines use the common reference method for EEG signal acquisition, but have the ability to redisplay the EEG in any montage required.

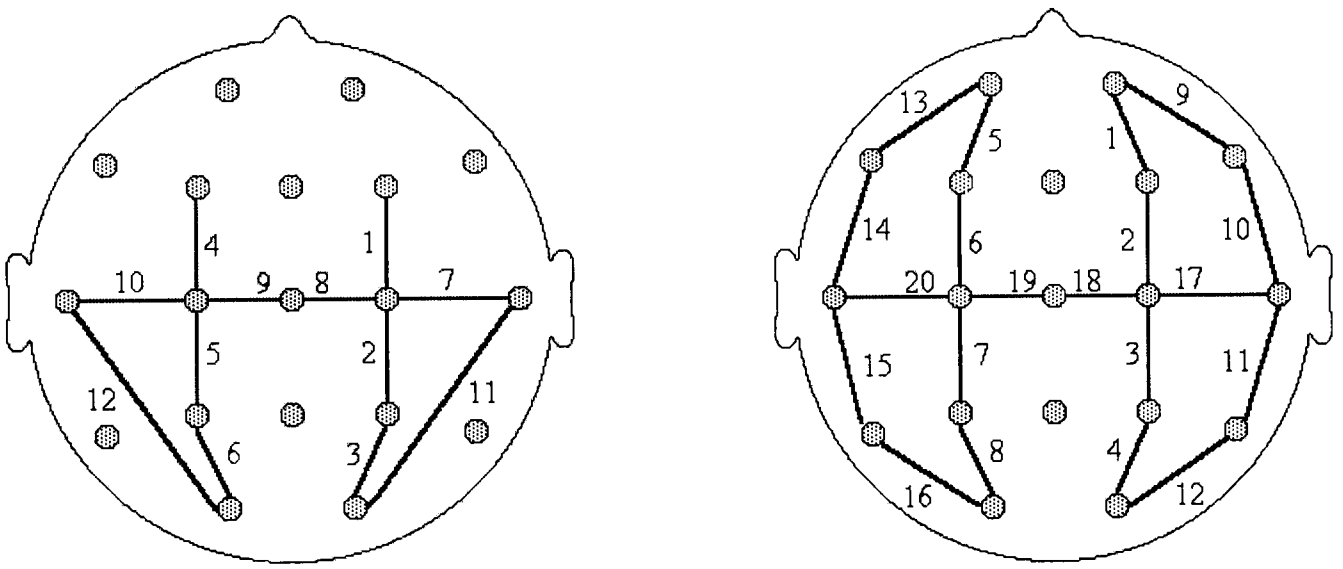


Figure 1.4: Examples of bipolar montages: a) Neonatal montage. b) 'Double Banana' montage often used in children and adults. In this study this montage without Cz was used.

1.3.4. Normal activity recorded in the EEG

The EEG is a gently fluctuating waveform with a fairly wide frequency spectrum. Different parts of the brain produce different waveform characteristics. The ongoing continuous pattern in the EEG is referred to as the background activity. This pattern is described in terms of its amplitude, frequency, symmetry and synchrony between both cerebral hemispheres. The frequencies in the EEG are split into frequency bands, which have individual characteristics. Berger in 1929 described the alpha (8-13Hz) and beta rhythms (> 13Hz) or waves. Grey Walter introduced the term 'delta

rhythm' to describe all frequencies below alpha rhythm and decided that those frequencies in the 4-7Hz range needed a special designation called theta.

Alpha activity (α)

Alpha activity is a frequency of activity from 8-13 Hz (Fig. 1.5). Alpha rhythm is the classical EEG correlate of relaxed wakefulness and specifically refers to the normal rhythmic activity of this frequency seen over posterior regions of the head on eye closure. It appears from the age of 3 years.

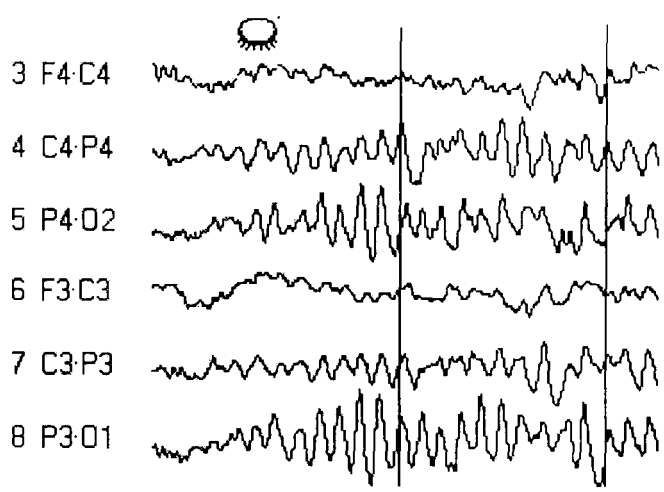


Figure 1.5: Alpha rhythm

The frequency reaches a mean of 10 Hz at the age of 10 years and may decline with advancing age. It is found most typically over the posterior regions of the head but may also be present in central and temporal regions. The rhythm is attenuated or abolished by visual attenuation and transiently by other sensory stimuli.

Beta activity (β)

Any activity in the EEG that has a frequency greater than 13 Hz is called beta activity (Fig. 1.6). It usually has an amplitude of less than 30μV. Activity with a frequency of 18-25 Hz is usually more conspicuous during drowsiness, light sleep, and rapid movement sleep (REM) than during wakefulness. Beta activity may be induced by a number of different drugs, particularly barbiturates and benzodiazepines. Excessive beta activity has recently been described in the EEGs of children with lissencephaly.

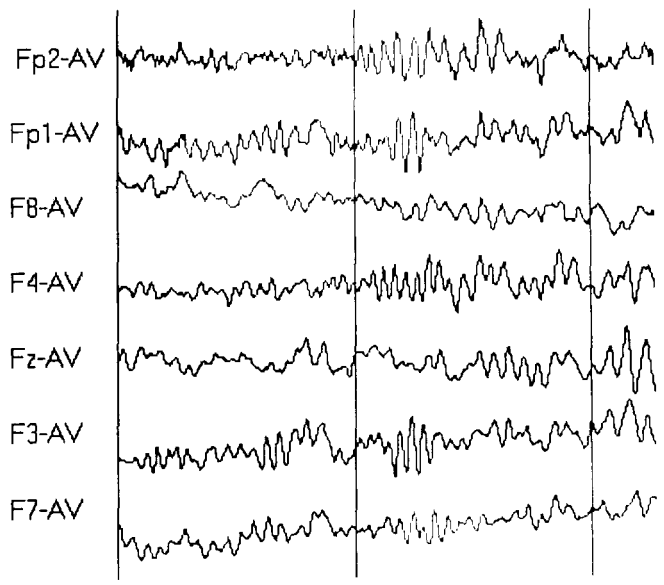


Figure 1.6: Beta activity over frontal

Theta activity (ϕ)

Activity with a frequency range of 4-7 Hz is termed theta activity (Fig. 1.7). The normal waking adult EEG contains very little theta activity; it only becomes evident during drowsiness and sleep. There is however considerable theta activity in the EEGs of children and infants. In very young children a dominant posterior theta rhythm is present which gradually matures to alpha rhythm.

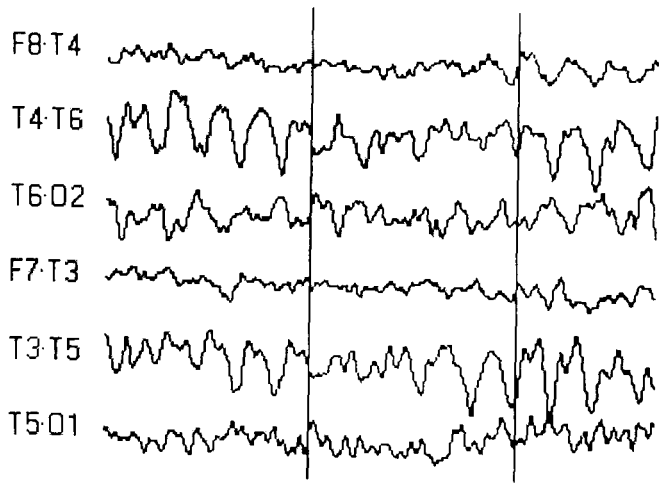


Figure 1.7: Theta activity

Delta activity (δ)

This is activity below 4 Hz. (Fig. 1.8). It is present during sleep in the normal adult and is the predominant EEG activity of the infant. Posterior slow waves of youth develop as slow transients after the first year of life, are maximal in the female at 5 years and in the male at 9 year, than decrease in the middle teens and are usually gone in the early twenties. Polymorphic delta activity is continuous irregular, slow activity that varies considerably in duration and amplitude with time, persists during sleep, and shows little variation with change in the physiological state of the patient. This activity can be found postictally in patients with epilepsy. It is commonly seen, with a localised distribution over destructive cerebral lesions involving subcortical white matter. It is also seen in patients with white matter encephalopathies. Delta activity may also be intermittent and rhythmic.

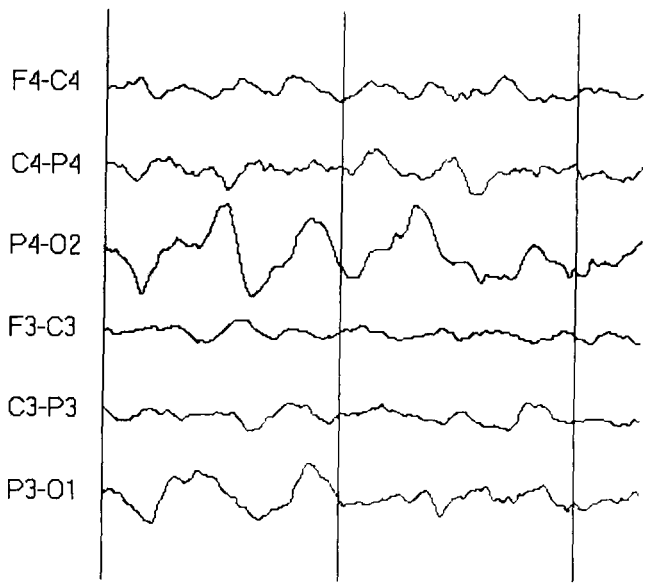


Figure 1.8: Posterior delta activity in a 2 year old boy.

1.3.5. Other types of EEG activity

Mu Rhythm (μ)

This is a type of activity that is sometimes seen over central regions, has a frequency usually in the alpha range and is arch shaped (Fig. 1.9). It is strongly related in a negative sense to motor movement, being blocked by movement, or the thought of movement. Its presence is not thought to have any diagnostic significance.

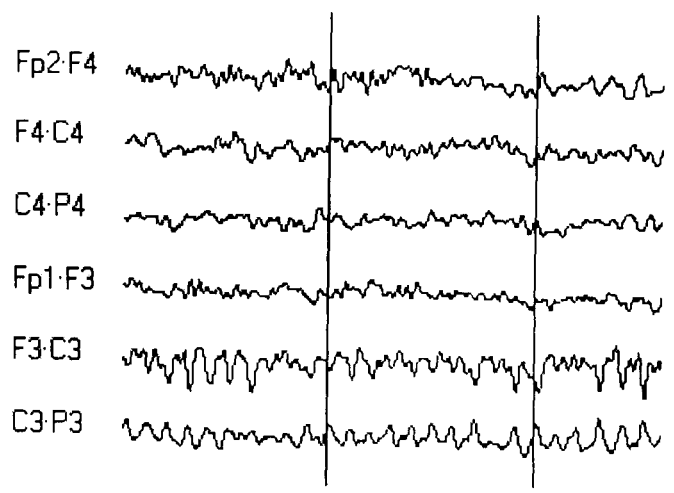


Figure 1.9: Mu Rhythm in a 7 y old girl

Lambda waves (λ)

These are well-defined electropositive sharp waves that can occur in the occipital region in normal subjects during visual exploration (Fig. 1.10). They are usually associated with very clear responses to varying rates of photic stimulation including single flashes. Lambda waves are most frequent in children and young adults.

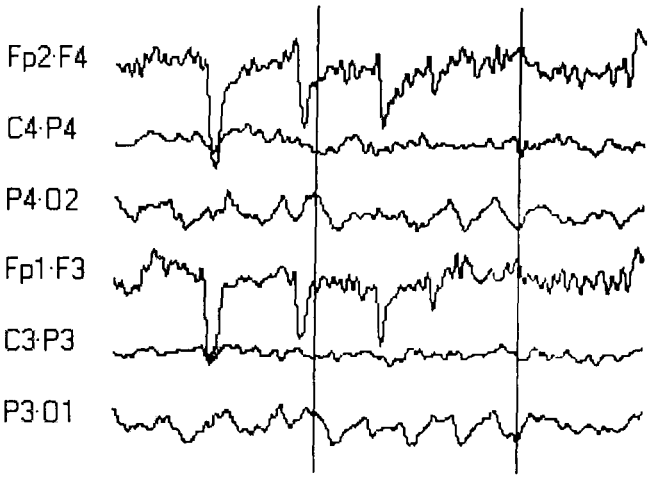


Figure 1.10: Lambda waves. Note eye movement artefacts

1.3.6. Maturation of the EEG

The development of the EEG from the newborn to the adult is not linear. The most abrupt changes occur between early prematurity and the first three months after term. The EEG of the premature baby depends less on the gestational age than the

corrected gestational age. After the first three months neonatal patterns are replaced by patterns which show different rhythms in different areas. From around six months of age mu-like rhythms are often prominent. This differentiation and the frequency of the rhythms increase fairly rapidly during the first year of life. Figure 1.11 summarises the development of the posterior rhythm during childhood. During childhood and adolescence the EEG develops rather steadily towards that of the adult with the exception of a few patterns which appear transiently during this time. The predominant background activity is between 5-8 Hz during wakefulness in children and 8-13 Hz in older children and adults.

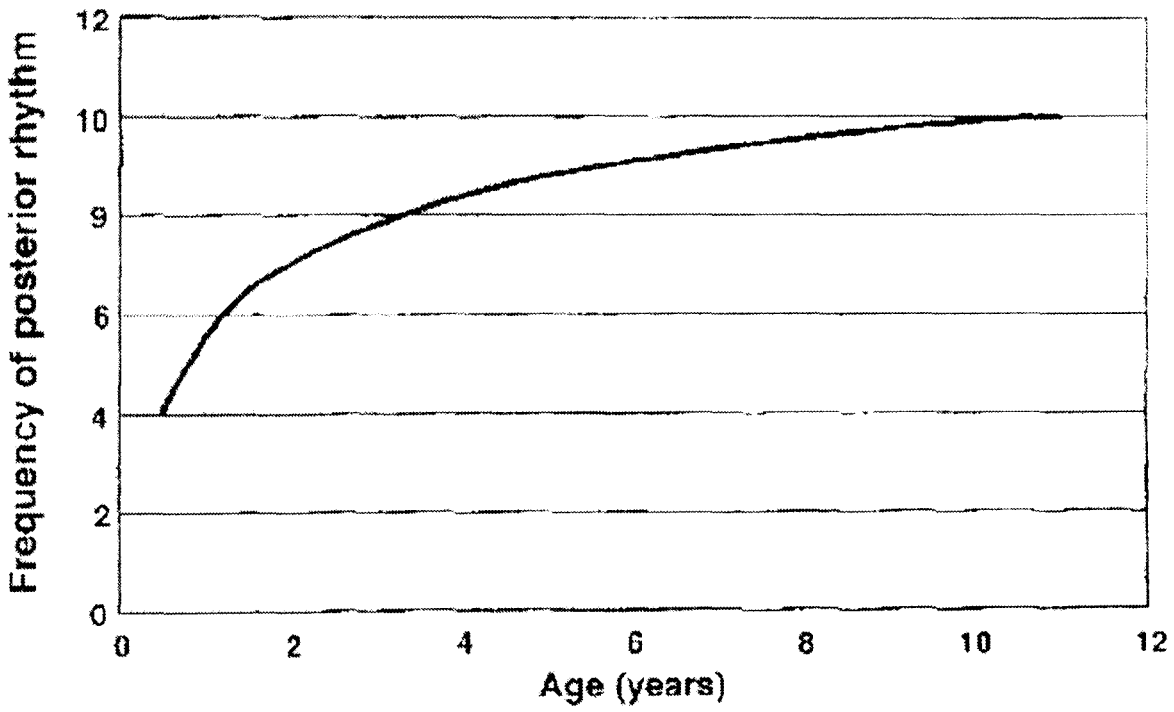


Figure 1.11: Normal maturation of posterior dominant rhythm (after Misulis and Head, 2003).

1.3.7. The Abnormal EEG in Epilepsy

The EEG is an indispensable investigation for the early assessment of epilepsy in infants and children. Abnormalities in the EEG may consist of epileptiform discharges, paroxysmal slow waves, background activity inappropriate to age or seizure discharges. Epileptiform discharges are sharp waves or spikes with or without associated slow waves. They are clearly distinguishable from the background activity and are usually surface negative. A spike is of shorter duration (< 70 msec) than a

sharp wave (70 - 200 msec) and may occur as polyspikes i.e. a group of spikes together. Slow waves may also be paroxysmal i.e. are clearly distinguished from the background activity and have an abrupt onset and termination.

Patterns seen on the EEG that are abnormal in adults may be normal in younger people. Synchrony, distribution and relation to sleep stages must be taken into consideration when deciding whether a wave form is normal or abnormal.

EEG is important for seizure classification, in particular to differentiate between symptomatic epilepsy in patients with structural brain lesions, cryptogenic epilepsies due to presumed but unproven pathology and idiopathic epilepsies arising in a structurally normal brain.

1.3.7.1. Ictal discharges

During an epileptic seizure, the EEG typically shows continuous rhythmic activity, often associated with spiky transients. The routine 20-30 min EEG rarely demonstrates clinical seizures. However, a notable exception is the hyperventilation induced absence seizure (Figure 1.12).

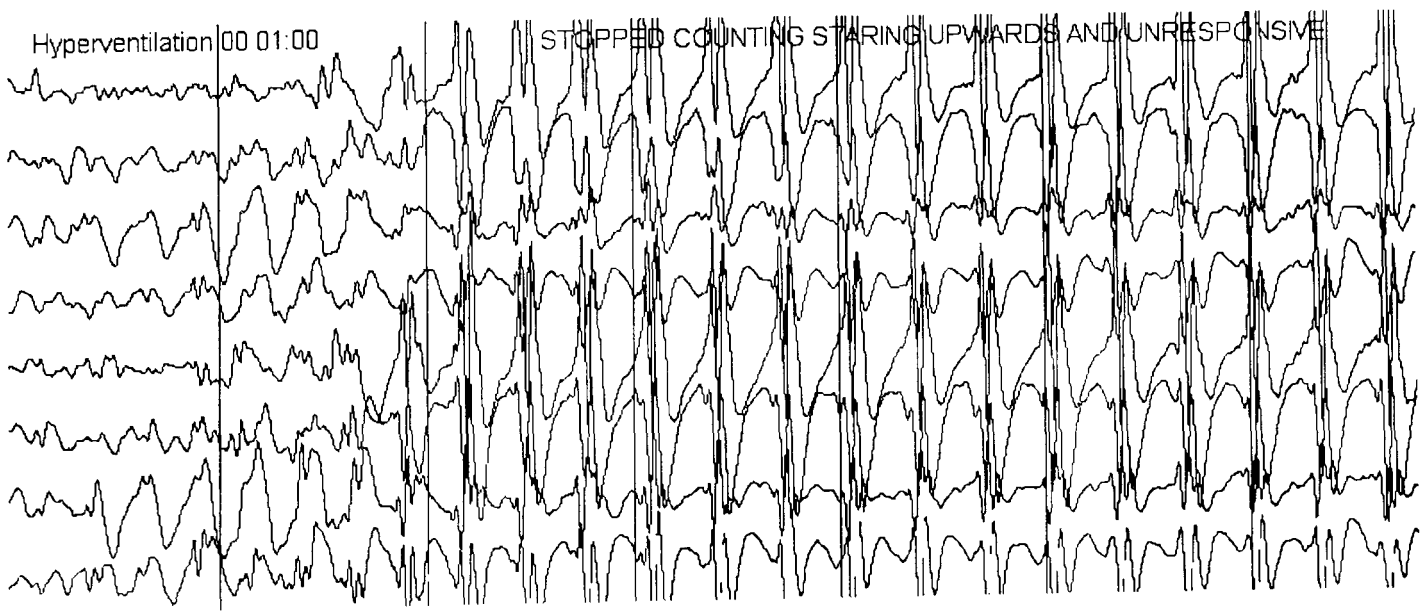


Figure 1.12: Absence seizure with typical 3 per sec spike and wave activity in a 7 year old girl occurring during hyperventilation. She stops counting, stares upwards and is unresponsive.

When a seizure is captured on EEG, seizure classification is much more accurate and in the case of symptomatic epilepsies, localisation of the seizure focus is often possible. Figure 1.13 shows a seizure in a 17 year old girl, who previously had demonstrated generalised interictal discharges without clear lateralisation. However, as can be clearly seen in Figure 1.13, during a complex partial seizure occurring during EEG recording a right fronto-temporal origin is evident.

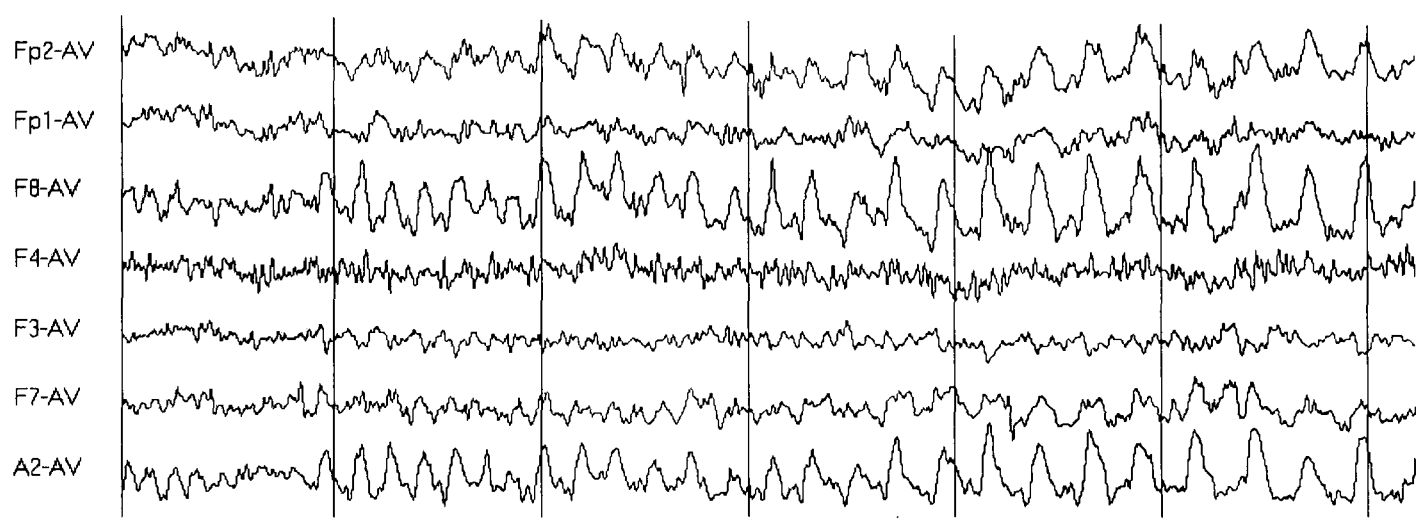


Figure 1.13a: Complex partial seizure in a 17 year old adolescent. Beginning of the seizure with rhythmical activity building up over the right fronto-temporal region. No clinical changes were seen at this point.

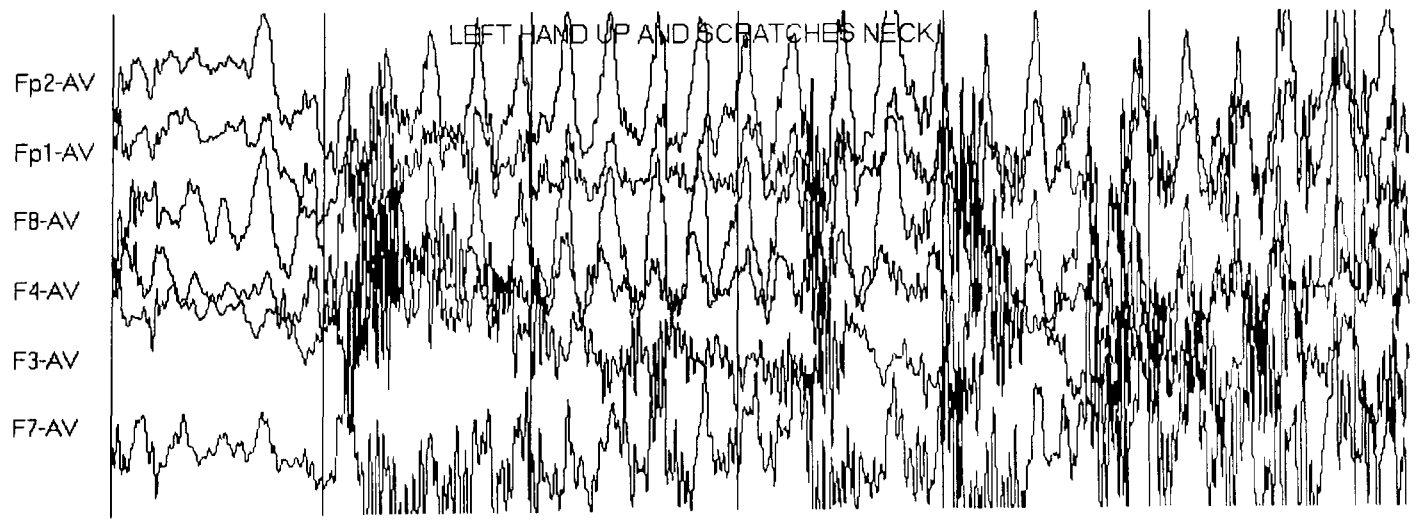


Figure 1.13b: After 18 seconds the patient lifts her left hand and scratches her neck. The EEG shows more widely spread discharges over the right side and generalised movement and muscle artefacts.

1.3.7.2. Interictal changes

Epileptiform discharges may also occur in the interictal state, between overt seizures and are more likely to be isolated or brief. They can be either generalised (Fig. 1.14) or focal (Fig. 1.15). These are usually referred to as subclinical epileptiform or interictal discharges. Interictal changes may also show non-epileptiform changes consisting of generalised or focal background abnormalities such as slow waves.

Aarts et al. (1984) classified a discharge as subclinical where 'the available methods of clinical observation, applied under particular circumstances, fail to show any changes in the patient'. This definition has been adopted by others and will be used in the following.

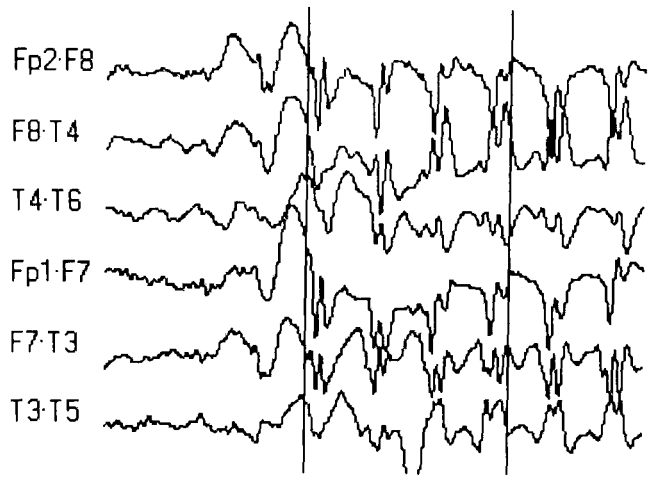


Figure 1.14: Generalised spike and wave without clinical correlate

Interictal discharges occur in up to 90% of patients with epilepsy, although they are not necessarily observed in every EEG recording (Ajmone Marsan and Zivin, 1970; Salinsky et al., 1987, Sundaram et al., 1990). Seizure type and aetiology do not seem to influence occurrence of ID (Salinsky et al., 1987, Sundaram et al., 1990) which can be present even when a patient has been seizure free for many years. Interictal spiking does not change before seizures but increase markedly after them, particularly after secondary generalised seizures (Gotman and Marciani, 1985).

The effect of anticonvulsant is still unclear. Ludwig and Ajmone-Marsan (1975) described activation of discharges after withdrawal of medication, whereas other studies showed no relationship between interictal discharges and anticonvulsants as carbamazepine, phenytoin (Rodin et al., 1974; Wilkus et al., 1978; Gotman and Marciani, 1985; Salinsky et al., 1987). An acute intravenous injection of phenytoin is, however, followed by decreased interictal discharges (Milligan et al., 1983).

Ludwig and Ajmone Marsan (1975) described activation of discharges after withdrawal of medication, whereas other studies showed no relationship between interictal discharges and AEDs (Duncan, 1987).

In fact, some drugs, for example carbamazepine, are known to cause no improvement or even deterioration in the EEG whilst improving seizure control (Wilkus et al., 1978). Rectal or intravenous diazepam (Milligan et al., 1982) as well as intravenous injection of phenytoin (Milligan et al., 1983) reduces interictal discharges. There is some evidence that phenobarbital (Frost, Jr. et al., 1986), sodium valproate (Adams et al., 1978) and lamotrigine (Binnie et al., 1986; Jawad et al., 1986; Besag, 1994) can reduce the number of interictal discharges. Ethosuximide reduces discharges in respect to diurnal 3 Hz spike wave activity only (Sato et al., 1982).

In benign epilepsy of childhood with centro-temporal spikes (BECT), the most common idiopathic epilepsy syndrome of childhood, interictal sharp waves (Fig. 1.15) occur in up to 70% of children with BECT during wakefulness and in almost all during drowsiness and sleep (Degen et al., 1988; Holmes, 1992).

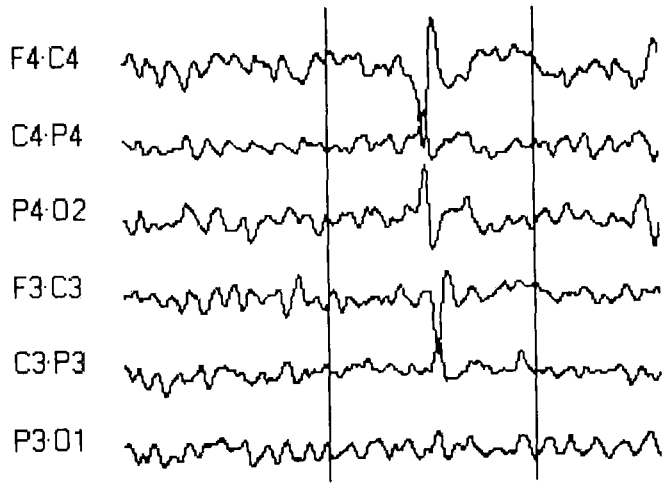


Figure 1.15: Rolandic sharp wave

Since many epilepsy syndromes have a genetic component it is not surprising that interictal discharges are also found in members of the families of children with epilepsy (Gerken and Doose, 1973). Possibly for the same reason Eeg-Olafson et al. (1971) found interictal discharges in 1 - 3.5% of children with no history of clinical seizures. Although such children were said to be neurologically normal, 50% of them showed some evidence of behavioural disturbances and up to 20% had severe learning difficulties.

1.4. Transitory Cognitive Impairment (TCI)

1.4.1. History and Definition

Shortly after the invention of electroencephalography, Berger (1933) showed that absence seizures were accompanied by high amplitude rhythmic spike and wave on the EEG. Gibbs et al. demonstrated as early as 1935 that these characteristic wave forms could occur without obvious clinical symptoms and named them 'larval discharges'.

Schwab (1939) developed new methods of studying the precise effects of these EEG phenomena on individuals. He tested the ability of patients who suffered from absence seizures to respond to auditory and visual stimuli during spike and wave discharges. Stimulus presentation and motor response were recorded simultaneously on a four-channel electroencephalograph so that the temporal relationship between them could be ascertained (Fig. 1.16).

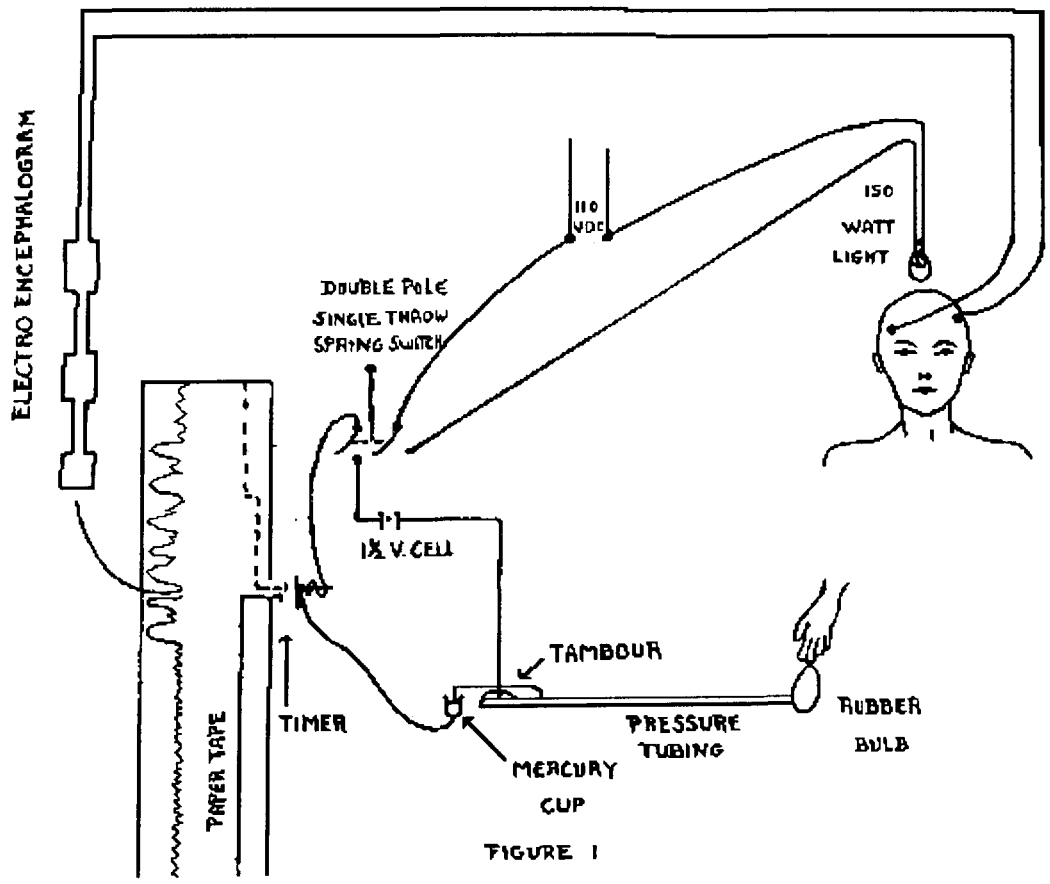


Figure 1.16: Schwab (1939): First TCI testing by means of a simple reaction time task: the patients had to press the rubber bulb as soon as the light was switched on.

Stimulus presentation was triggered manually by the examiner as soon as he saw a discharge on the EEG. In addition the patient was given a number of stimuli when no EEG abnormalities were apparent, so that reaction times with and without discharges could be compared. Thus each patient acted as his or her own control, nullifying critical confounding factors such as age, education, concomitant learning difficulties, seizure frequency and medication. It was found that if there was any response at all to a stimulus given during a discharge the reaction time was longer than to stimuli presented at other times. Duration of reaction times varied roughly in proportion to the length of the bursts seen in the EEG, and often no response at all was associated with the longer bursts. Schwab concluded that he had demonstrated six levels of impairment of consciousness as reflected in various degrees of prolonged reaction times.

In 1984 Aarts and colleagues used a computerised version of the CORSI Blocks test (Corsi, 1972). The patient was presented with an array of coloured blocks on the screen which flashed in a random sequence; he or she was then required to replicate the whole sequence using a light pen. In the verbal version a sequence of words appeared followed by a list of words from which to choose the correct words in sequence. In a newer version a touch screen instead of the light pen is used. As in Schwab's experiment, performance in trials with subclinical discharges was compared with that during trials without discharges in the same patient. A significant impairment of performance was found during trials with discharges in half the patients tested. Aarts et al. termed this brief and transient cognitive deficit during subclinical epileptiform discharges 'transitory cognitive impairment' (TCI).

1.4.2. Frequency of TCI in Persons with Epilepsy

It is important to note that many of the early studies following Schwab's discovery did not differentiate between pure subclinical EEG activity and minor seizures without motor concomitants such as absences (Shimazono et al., 1953; Kooi and Hovey, 1957; Tizzard and Margerison, 1963a; Mirsky and Van Buren, 1965; Ishihara and Yoshii, 1967; Goode et al., 1970). Some authors were merely interested in

responsiveness during generalised spike and wave discharges (Porter et al, 1973; Brown et al. 1974) and never actually claimed to investigate subclinical discharges, an assertion claimed subsequently by others on their behalf. Indeed, Kooi and Hovey (1957), Ishihara and Yoshii (1967) and Goode et al. (1970) described automatism during generalised spike wave activity in some of their patients: "*Only one patient demonstrated extended three-per-seconds generalised spike and wave bursts. These were associated with staring, rhythmical twitching of the eyelids and loss of neck tone. This patient did not respond to any question asked during a burst until after the paroxysmal activity subsided*" (Kooi and Hovey, 1957).

Thus, in some reports cognitive functioning during absences, rather then that during subclinical epileptiform discharges was measured. Yeager and Guerrant (1957) were probably the first to describe behaviour during EEG abnormalities with an attempt to distinguish between clinical and subclinical effects. As the probability of recognising an absence seizure and of detecting a cognitive deficit both increase with the duration of discharge, it is imperative to observe patients carefully, either with the help of video monitoring (Aarts et al., 1984) or on a one-to-one basis. Since this issue has been taken into account the number of patients with typical 3 Hz spike and wave activity reported in TCI studies has dropped dramatically. It has been suggested that interictal discharges probably do not occur in typical childhood absence epilepsy (Delgado-Escueta, 1979).

Two exceptions were unable to confirm significant impairment of cognition during discharges (Prechtl et al., 1961; Aldenkamp et al., 1996). Prechtl et al. (1961) used a choice reaction time task with simultaneous EEG recording, in which five lamps lit up in random order. The patient had to push a corresponding button to turn the light off, which triggered the next light's onset. Neither generalised nor focal discharges increased error rate or reaction time in 12 epileptic patients. However, the mean and variance of the interval between correct stimulus and correct response were significantly higher during paroxysmal and diffuse flattening of electrical activity than during normal electroencephalic activity.

Using the CORSI test described earlier (Aarts et al., 1984) Aldenkamp and colleagues (1996) compared cognitive function in three different groups each of 20 children with epilepsy who were considered seizure free: (1) without evidence of EEG discharges, (2) with subclinical epileptiform discharges, (3) with subtle seizures revealed by intensive video monitoring techniques. While they found no significant impairment of cognition in the group with subclinical discharges only, the third group of children showed poorer test results associated with the subtle seizures. Thus they were unable to confirm TCI, but rather demonstrated cognitive impairment during short and subtle seizures. Unfortunately they gave no information as to how the data was analysed nor the data itself. It also remains unclear whether the duration of discharges were comparable between the groups. Furthermore, it appears that most of their patients did not have sufficiently frequent discharges (i.e. 1 discharge every 1 - 3 minutes) to allow statistical analysis looking for TCI to be performed. Nevertheless, they claimed that TCI "may thus be an artefact, caused by the inadequacy of video monitoring techniques". The flaw in this argument is that TCI is detectable as a result of enhanced monitoring techniques. It appears merely a question of the technique used and not of content.

Some 50 studies have confirmed the occurrence of TCI in about 50% of patients investigated (Kooi and Hovey, 1957; Tizzard and Margerison, 1963a; Goode et al., 1970; Hutt and Gillbert, 1980; Aarts et al., 1984; Binnie et al., 1987; Kasteleijn-Nolst Trenité et al., 1988; Rugland, 1990; for a review see Binnie 2003). However, it has become clear that the detectability of TCI in a single patient is dependent on various factors. Multiple interactions between these factors exist (see Fig. 1.17), which are often complex and overlapping and will be discussed in more detail later.

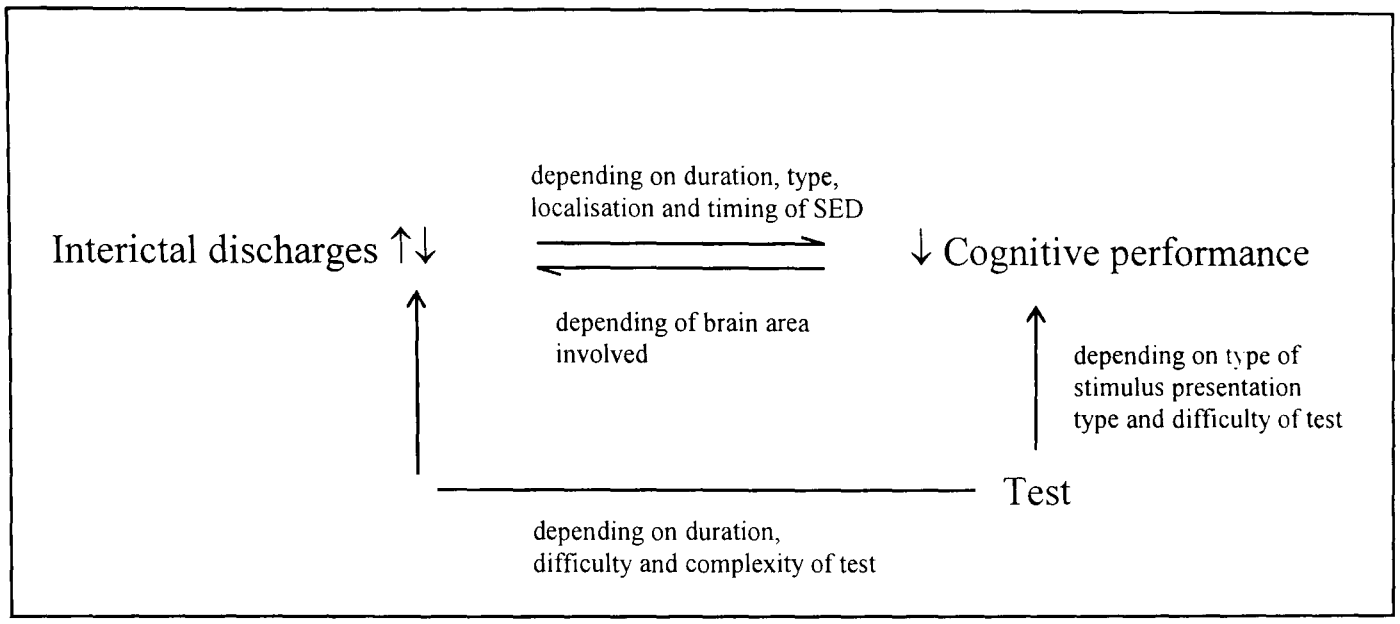


Figure 1.17: Interaction between subclinical epileptiform discharges, neuropsychological test and cognitive function.

1.4.3. Interaction between Discharge and TCI

1.4.3.1. Effect of Duration of Discharge on TCI

The duration of the epileptiform paroxysm is one of the most frequently reported factors influencing the detection of TCI: the longer the discharge the more likely it is to impair performance, (Kooi and Hovey, 1957; Davidoff and Johnson, 1964; Goode et al., 1970; Sellden, 1971; Aarts et al., 1984; Sengoku et al, 1990; Opp et al, 1993). Depending on the test used, different critical thresholds have been described below which no consistent impairment could be detected: 2 seconds (Tizard and Margerison, 1963a; Geller and Geller, 1970), 2.5 seconds (Sellden, 1971), 3 seconds (Goode et al., 1970; Opp et al., 1992). Only Browne et al. (1974) could not find a threshold under which no impairment was seen. However, as mentioned above, his patients probably had a mixture of clinical absences and subclinical generalised 3 per second discharges.

There are some reports describing TCI during discharges shorter than 3 seconds in single patients (Tizard and Margerison, 1963; Rugland, 1990; Shewmon and Erwin, 1988 a). Aarts et al. (1984) and Rugland (1990) even found TCI during single spikes.

but until recently no studies have specifically addressed the effect of very brief discharges. Provinciali et al. (1991) examined the effect of brief generalised discharges on shape recognition in 15 patients and found a significantly increased error rate during discharges in 9 patients. They did not find the duration of the discharges to be influential, and both discharges of < 1 second and of < 2 seconds being equally likely to be associated with TCI. Pressler (1997) found evidence of TCI during both focal and generalised discharges of 1 -3 seconds duration using a choice reaction time test with EEG triggered stimulus presentation (see chapter 1.4.4.1).

1.4.3.2. Effect of type of discharge on TCI

Most of the early investigators studied the influence of generalised spike and wave activity on cognition (Schwab, 1939, 1941; Tizard and Margerison, 1963; Goode et al., 1970; Porter et al., 1974). No significant difference was found when comparing the effect of typical 3 Hz spike and wave discharges with that of atypical generalised spike wave discharges (Davidoff and Johnson, 1964). Browne et al. (1974) graded the 'generalisation' of 3 Hz spike and wave discharges according to the distribution of the amplitude and found that both incomplete and complete generalised discharges were followed by prolonged reaction times, although the degree of impairment was more marked when discharges were fully generalised. Hutt and colleagues (1977) examined the effect of different types of EEG activity on reaction time in 20 children with epilepsy. They found that bilateral spike-wave discharges have an effect less than that of generalised discharges, but greater than those for localised spike-wave discharges or for slow waves. Analysis of variance was performed with ensemble size and type of EEG activity as main variables and both were found to have significant effect. Performance during generalised activity was significantly worse than during all other types of EEG activity, while there was no significant difference between bilateral spike and wave activity. Generalised bursts of delta or theta activity were apparently associated with TCI in only a few patients (Aarts et al., 1984).

During focal discharges either non significant impairment has been reported by a number of investigators (Tuvo, 1958; Prechtl et al., 1961; Sellden, 1971; Hutt et al.,

1977; Opp et al., 1993) or TCI was found as an exception only (Kooi and Hovey, 1957).

In contrast, Aarts et al. (1984) found TCI during focal discharges in more or less the same frequency as during generalised discharges. This might be because the CORSI test is more demanding that most of the other tests used (see below). Since then, TCI during focal discharges has been confirmed by others (Kasteleijn-Nolst Trenité et al., 1988; Binnie et al, 1992; Shewmon and Erwin, 1988a and b; Pressler, 1997).

It has been suggested that even spikes which cannot be detected using scalp electrodes may interfere with cognitive function. Krauss et al. (1996) examined patients who had bilateral depth electrodes implanted to evaluate intractable temporal lobe epilepsy. On a verbal and a visuo-spatial memory task, six out of eight patients showed a significant decrease in working memory performance during mesial temporal spiking, the greatest disruption to spatial and verbal recall being associated with left hippocampal spikes. As discharges were not apparent on surface recording TCI would have been missed in these patients.

1.4.3.3. Effect of lateralisation and localisation

It is well known that the lateralisation and localisation of epileptogenic foci has an effect on cognition and learning. Left sided foci in right-handed patients are associated with impairment of reading skills (Stores and Hart, 1975) and verbal memory (Hermann et al., 1987), whereas foci on the non-dominant side are more likely to cause impairment in visuo-spatial tasks (Mirsky and Van Buren, 1965).

Aarts et al. (1984) confirmed the existence of such a correlation with respect to TCI using verbal and performance versions of the CORSI test. They demonstrated that right sided discharges were more likely to produce TCI in the non-verbal version than were left-sided ones. Left sided discharges were likewise associated with TCI in the verbal version.

Shewmon and Erwin (1988) investigated three patients with frequent spikes using a visual reaction time task and showed not only localised effects of occipital spikes on reaction times, but also that this effect was more pronounced when the stimulus was presented in the contralateral visual field or the response made with the contralateral hand. Thus, several specific tests are needed to distinguish between disturbances of different cognitive functions.

1.4.3.4. Time of Occurrence of Discharges

It appears that discharges have most effect when they occur during stimulus presentation. Mirsky and Van Buren (1965), using a delayed identification task, showed that the impairment was greatest when discharges occurred during stimulus presentation, and also when discharges occurred during the second prior to the onset of the stimulus. Binnie et al. (1987), using the CORSI test described above, studied this matter in further detail in 91 patients and found that discharges disrupted performance most when they occurred during stimulus presentation, followed by those occurring during the stimulus-response interval and in the 2 seconds preceding the stimulus presentation. Discharges occurring only during the response phase did not produce a significantly increased error rate.

One problem in investigating very brief discharges is that they may not occur in sufficient number during stimulus presentation to demonstrate an effect. By using an EEG triggered stimulus presentation, the stimulus is thus spike-locked and a more precise time correlation can be established. Pressler (1997) examined 11 children with focal (n = 7) and generalised (n = 4) EEG discharges lasting less than three seconds with a choice reaction time task with stimuli triggered by discharges. In 8 out of 11 patients, reaction times during discharges were significantly prolonged compared to trials without discharges. There was no correlation between the duration of discharges and the likelihood of measuring TCI. Even in patients with very brief focal discharges, with a maximum duration of less than 1 second, TCI was found in 2 out of three patients. It is likely that the exact correlation in time between discharge

onset and stimulus presentation was responsible for the high number of patients displaying TCI during focal and very short discharges.

1.4.4. Interaction between Cognitive Testing and TCI

1.4.4.1. Type of Stimulus Presentation and Task Continuity

Various methods of tasks have been used in TCI testing, including continuous (Aarts et al., 1984, Binnie et al., 1992), EEG triggered (Schwab, 1941) or intermittent EEG triggered stimulus presentations (see below) (Binnie und Lloyd, 1973; Porter et al., 1973; Shewmon and Erwin, 1988a; Sengoku et al., 1990; Pressler, 1997).

A continuous task is the most widely used method (Tizard and Margerison, 1963a; Goode et al., 1970; Aarts et al., 1984; Binnie et al., 1987; Porter et al., 1973): EEG recording and a neuropsychological test presenting the stimuli in sequence, requiring more or less continuous attention from the patient, are performed in parallel connected either by pen box or digital interface so that stimuli presentation and response of the patient are marked on the EEG record.

However, tests like the 5-light test (Tizard and Margerison, 1963a and b) or the CORSI test (Aarts et al., 1984; Binnie et al., 1987) are 'continuous' in that continuous attention is required, but both, the stimulus presentation and the required response are discrete. Truly continuous performance monitors, such as Goode's pursuit rotor (Goode et al., 1970) or a newer computerised tracking task (Opp et al., 1992) appear optimal because there is a complete correlation between the occurrence of spikes and performance. In both studies only generalised discharges of 3 seconds or longer disturbed performance significantly. On-going performance can probably be continued undisturbed during brief or focal discharges (Opp et al., 1992). Therefore tracking tasks are not useful for the clinical evaluation of TCI.

An intermittent task (stimulus presentation with long gaps in between) has the drawback that changes in arousal can occur between stimulus presentations. This

may cause fluctuations in test results, which is particularly relevant in children with a short attention span.

EEG triggered stimulus presentation on its own (stimulus presentation each time a discharge is detected) as used by Schwab (1939) insures a constant time relationship between stimulus presentation and discharge. However, EEG triggered stimulus presentation carries the risk that discharge probability is influenced by the state of arousal. Thus, a decrease in awareness may cause both the epileptiform discharges and the cognitive impairment.

This problem can be reduced by presenting intermittent stimuli in addition to the EEG triggered presentations (Shewmon and Erwin, 1988a; Pressler, 1997). These intermittent presentations have to be randomised in order to avoid presenting any possible timing clues to the patient as to whether a presentation is triggered or not. Nevertheless, triggered stimulus presentation remains problematic as it is difficult to exclude an effect of alertness on discharge frequency. As discharges are more likely to occur during time of reduced alertness, impairment found in test with EEG triggered stimulus presentation may be due to fluctuations of alertness rather then TCI (Aarts et al., 1984; Binnie and Marston, 1992).

1.4.4.2. Type of Task

Failure to detect TCI can be dependent upon the type of cognitive test used. Simple motor tasks such as rhythmic tapping (Shimanzono et al., 1953; Tizard and Margerison, 1963a; Davidoff and Johnson, 1964; Mirsky and Van Buren, 1965) are relatively unaffected by discharges, whereas tests involving higher cortical functions are usually more susceptible. Tasks testing working memory are believed to be particularly sensitive (Tizard and Margerison, 1963a; Aarts et al., 1984; Hutt and Fairweather, 1975; Krause et al., 1997). The CORSI test, a test for verbal and visuo-spatial short term memory described earlier has been proven to be sensitive to subclinical epileptiform discharges. It is the test most widely used in the literature for

TCI testing and can be regarded as a gold standard, showing TCI in 50% of patients investigated, during both focal and generalised discharges (Binnie, 2003).

It is well known that when children who suffer from absences are called during an absence they sometimes answer adequately immediately after the seizure has ended (Shimanzono et al., 1953), suggesting that although the reaction time may have been prolonged, perception and memory of a question was not affected by the absence. Although simple reaction time is rarely disturbed due to discharges (Shimanzono et al., 1953; Tizard and Margerison, 1963a; Davidoff and Johnson, 1964; Mirsky and Van Buren, 1965), it has been suggested that complex or choice reaction times are more sensitive to TCI (Mirsky and Van Buren, 1965). This was confirmed by others (Hutt and Fairweather, 1975; Pressler, 1997).

Sellden (1971) used a binary choice task to investigate generalised and focal spike-wave discharges. All stimuli were presented randomly with respect to the bursts. While focal discharges caused no impairment in performance, generalised paroxysms produced significantly more errors but only if the duration was equal to, or longer than, 3.5 seconds. The reaction time during discharges was a significantly delayed if the discharge exceeded 2.5 seconds. However, the test applied was quite simple and patients were tested for only 6 minutes (see chapter 1.3.5.2).

1.4.4.3. Complexity and Difficulty of Task

The influence of the type of test of cognitive function overlaps with the degree of difficulty of the task itself. Using a digit-span test in children with photosensitive epilepsy Hutt (1972) found that recall of a sequence of digits was impaired if the presentation of the final digit was followed by a 1 or 2 seconds burst of generalised spike-wave activity evoked by a flashing light. The degree of impairment was a function of the number of digits in the sequence - sequences containing one or two digits less than the normal span according to age were less likely to be affected by spike and wave discharges than were longer sequences.

This was confirmed by Binnie et al. (1987) using the CORSI test, who found a non-specific effect of task difficulty. At a sequence length, which could be reproduced with few errors in the absence of discharges, epileptiform activity had little effect on test performance. TCI was demonstrable only, or more readily, when the level of performance required was close to the patient's individual limit.

Sengoku et al. (1990) tested a boy with Lennox-Gastaut syndrome using different reaction time tasks during EEG-triggered stimulus presentation. Although simple reaction time was prolonged by bursts of generalised spike and wave (a mean of 0.42 sec during discharges compared to a mean of 0.34 sec in their absence) this difference was even more marked in a choice reaction time task (mean of 1.23 sec during discharges compared to a mean of 0.69 sec in their absence).

1.4.5. Interaction between Cognitive Test and Discharges

1.4.5.1. Test Situation

In general there appears to be a bi-directional interaction between epileptiform discharges and cognitive function: cognitive testing itself increases concentration and thus reduces epileptiform activity. It is well known that different stimuli can block absence seizures. In other people, stress or concentration may increase epileptiform discharges or even seizure activity (Altafulla and Halgren, 1988). Kooi and Hovey (1957) administered the Wechsler Adult Intelligence Scale with synchronous EEG recording in 21 patients with subclinical EEG discharges. At rest with eyes closed they found interictal discharges in 4.9% of patients, with eyes open in 3.7% and during testing in only 2%. Suppression of discharges during cognitive testing was consistent in all patients with generalised discharges, while this effect was highly variable in patients with focal discharges.

In another study including both children and adults, 45% of patients showed a reduction and 16% showed an increase in epileptiform activity, during the testing compared to during a base line period (Rugland, 1990). In contrast, Kasteleijn-Nolst

Trenité et al. (1988) showed that discharge rate in children was lower at rest than during the performance of scholastic skills.

1.4.5.2. Duration of Test

Kooi and Hovey (1957) attempted to ascertain whether discharges occurred more frequently during some parts of the question-response period than with others. The trend was toward a higher proportion of activity during questions and between questions and responses, than during the response itself. Suppression of discharges was greatest near the beginning of each subtest when a fresh task or set of questions began and was least between the end of the response and the start of the next question. This suggests that a task needs to be presented for a sufficiently long time to measure TCI, since it appears that discharges will be suppressed at the beginning of testing.

1.4.5.3. Difficulty of Task

In addition the difficulty of the tests plays a role. Tizard and Margerison administered a simple recognition task (tape test) and a choice reaction time test (5-light test, similar to the test described by Prechtl et al. (1961)) daily to two patients for 10 days. In the tape test the subject had to listen to a recorded series of random numbers, read at a rate of 2 per second. The task was to press a bulb as soon as possible when the number 6 was heard. As well as investigating the effect of discharges on error rate and reaction time (see above) they were interested in the effect of different test situations on spike-wave activity (Tizard and Margerison, 1963B). In both patients, significantly fewer discharges were recorded during the 5-light test than at rest and significantly more during the tape test than at rest. Both patients agreed that the 5-light test was much more interesting than the tape test. The authors postulated that not only a change in arousal (which should have been accompanied by a change in

autonomic function and background activity, but was not), but also the state of divided attention may contribute to changes in discharge frequency.

Hutt (1972), using the tape test in three different levels of difficulty in children with epilepsy confirmed that when the child is 'bored' there is a greater likelihood of discharges in the EEG. Conversely, he also showed that when the task passes a critical level of difficulty, the amount of discharges strongly increases again.

Ounsted et al. (1963) describes the relationship between test difficulty and epileptiform activity as U-function: a minimum of discharges in between the minimum and maximum of the degree of difficulty. Thus, a test should make demands on the upper limit of a patient's capability to ensure that discharges are not suppressed and that the test is sufficiently complex and difficult to demonstrate TCI.

1.4.5.4. Localisation of Discharges

Until recently the effect of arousal and cognition on EEG activity was believed to be non-specific. However in one study, during reading, epileptiform discharges occurred relatively less frequently and with a shorter duration over the left hemisphere than the right (Kasteleijn-Nolst Trenité et al., 1990). It seems that cognitive tasks suppress epileptiform discharges when they activate a region of the brain within the epileptogenic zone (Binnie, 1993). However, discharges from other epileptogenic zones not directly activated by the task are increased (Kasteleijn-Nolst Trenité et al., 1990). This may explain why these authors found an increase in discharges during performance of scholastic skills in an earlier study: selectively more discharges occurred over the hemisphere less activated by the task.

1.4.6. TCI in benign partial epilepsy

Although the definition of benign partial epilepsy is not fully defined (Lerman and Kivity, 1991), the diagnostic criteria proposed include no neurologic or intellectual

deficit; family history of epilepsy; onset of seizures after the age of 2 years; brief seizures that are stereotyped in clinical manifestation; frequent nocturnal manifestation and spontaneous remission in adolescence (Fejerman and Di Blasi, 1987; Dalla Bernardina et al., 1992; Lerman and Kivity, 1991). The principal EEG criteria include normal background activity, spikes or sharp waves with a particular morphology and localisation, activation of epileptiform activity during sleep but not during hyperventilation and occasional generalised spike and wave discharges (Fejerman and Di Blasi, 1987; Dalla Bernardina et al., 1992). The classification of the International Classification of Epilepsies and Epileptic Syndromes (1989) recognises two idiopathic, benign localisation-related epileptic syndromes in childhood: benign childhood epilepsy with centro-temporal spikes (BECT) and epilepsy of childhood with occipital paroxysms (EOP). In addition Aicardi and Chevrie (1982) described an atypical form of Rolandic epilepsy called atypical benign partial epilepsy (ABPE) with a similar clinical course with seizures difficult to treat and cognitive and behavioural problems common.

BECT is one of the most common epileptic syndromes accounting for 15-25% of childhood epilepsy (Cavazzuti, 1980). It is an age-dependent syndrome with an age of onset between 3 and 13 years and a spontaneous remission in all cases around puberty. In general seizures are rare and are usually orofacial simple partial seizures with or without secondary generalisation. The EEG typically shows frequent focal triphasic sharp waves followed by a slow wave over the centro-temporal region. These discharges have a tendency to spread and may shift form one hemisphere to the other. It is believed that 50% of children with a Rolandic focus as described above never have overt clinical seizures (Doose and Baier, 1989). Rolandic discharges are found in 1-3% of healthy children (Eeg-Olofsson et al., 1971; Cavazzuti et al., 1980) and in up to 30% of siblings of children with BECT (Doose and Baier, 1991).

Treatment of Rolandic seizures is still an issue of controversy. Treatment with carbamazepine, sodium valproate or phenytoin did not alter seizure frequency, seizure recurrence and duration of active epilepsy in a retrospective study involving 10 children without treatment and 20 children with (Ambrosetto and Tassinari, 1990).

Mental retardation, and/or neurological deficits are, by definition, lacking. However, several studies have reported impaired cognition and behaviour (Heijbel and Bohman, 1975; Piccirilli et al., 1994; Weglage et al., 1997). Causes for these neuropsychological deficits are likely to be multifactorial and prolonged nocturnal discharges, hereditary cerebral maturation disorder causing both the cognitive problems and the discharges (Doose, 1993; Doose et al., 2000). Finally, Colin Binnie and co-workers were the first to test a group of 10 children with BECT for transitory cognitive using the spatial version of the CORSI test (Binnie et al., 1992; Binnie. 1993). Seven children had typical BECT; of the other three, one exhibited typical Rolandic spikes, but had no known seizures, one had diurnal absences only, and the other developed seizures which were not typical of BECT after the first EEG recording. Six of the seven subjects with typical BECT exhibited an increased error rate during EEG discharges; this association was significant in four, in the others the trend was strong but not significant, as the number of discharges was small. Only one of the three children with atypical BECT showed TCI. Behavioural or cognitive problems were reported in most of the children including all of those with significant evidence of TCI. One child with bilateral discharges also performed the verbal version of the CORSI. This totally suppressed the left-sided discharges, and the verbal performance was unaffected by the right-sided discharges. During the non-verbal task, discharges continued on both sides, but TCI were seen only in association with those on the right. The authors concluded that, although by definition BECT does not cause cognitive deficits, TCI might have an adverse effect on psychosocial function in this condition, as indeed all the children in this study with TCI had behavioural or cognitive problems.

1.4.7. Clinical Relevance of TCI

An important practical issue is whether TCI materially impairs day to day psychosocial function and if so whether drug treatment to suppress discharges is either desirable or effective (Binnie 2003). Here the term, 'psychosocial dysfunction', implies disturbance within the patient's educational and social framework.

Only few investigations have addressed these issues. Discharges were accompanied by a significant increase in errors in 4 out of the 6 subsets when the Revised Amsterdam Children's Intelligence Test was applied to groups of children with epilepsy under continuous EEG and video monitoring (Siebelink et al., 1988). Furthermore, children with discharges during the IQ test showed an abnormal test profile. The same authors were interested in the effects of discharges in day to day cognitive performance in children, namely school performance such as reading and maths (Kasteleijn-Nolst Trenité et al., 1988). The occurrence of discharges was associated with an increased rate of errors per word read. Interestingly the children were actually reading faster during discharges, but less accurately, no hesitations being observed by the examiner. The possible relevance of TCI to daily life was further highlighted by a study of the effects of subclinical discharges on driving a motor car (Kasteleijn-Nolst Trenité et al., 1987). During discharges there was a significant increase in variance of lateral position on the road (i.e. the drivers either swerved or failed to follow the contours of the road). There are thus grounds to expect that TCI can have an adverse effect on a range of functions necessary for normal psychosocial performance.

1.4.8. Neuropsychological Explanations

Some general suggestions have been generated by this rather heterogeneous collection of studies: Tizard and Margerison (1963 a) postulated that subclinical bursts of spike and wave activity reduce the information handling capacity of patients with epilepsy.

Another hypothesis has been that generalised spike and wave activity functions as neuronal noise reducing the child's "rate of gain or information" or "channel capacity". A choice reaction time task can broken down into four sub-units corresponding with each of four successive stages of information processing (Smith, 1968): (1) time for registration of the stimulus; (2) time for recognition of the stimulus; (3) time for organisation of response, e.g. decision time; (4) time of execution of response. In a numerals-keys serial choice RT task with three levels of

difficulty it was found that RT was significantly longer during spike and wave than during background EEG (Hutt et al., 1977). The response time during discharges increased more with increased level of complexity of the task than the response time without discharges. The authors concluded that whilst interictal discharges may affect all stages of choice reaction time to some extent, decision (stage 3 above) seems to be the most sensitive stage in the progress to be affected (Mirsky et al., 1973; Hutt. 1977). Many gradations of performance in information processing and short term memory are possible, depending upon the demands of the task in question. According to the authors, spike waves behave as a kind of neuronal noise, whose effect is to reduce the patient's information-handling capacity. If the task is well within the patient's normal capacity, little or no change may occur during spike wave discharges. If, however the task is one at the very limits of the patient's normal capacity, a severe decrement in performance will occur.

1.4.9. Practical Implications

It is generally agreed by neurologists and paediatricians that patients should be treated for epilepsy only if they have clinical seizures. Treating the EEG, so called 'EEG cosmetics', is generally not practised. However, some single observations and uncontrolled trials revealed an improvement of cognitive functioning by suppressing discharges with AEDs in patients with established TCI (Aarts et al., 1984; Rugland, 1990).

A preliminary controlled trial was completed at St Piers Lingfield, a residential school for children with epilepsy and special needs (Marston et al., 1993). Ten children aged between 10 and 18 years completed the study; all had frequent subclinical discharges. A double-blind placebo-controlled crossover design was used. the active treatment being individually planned, taking account of the medical history and current medication, with the aim of suppressing epileptiform activity. Psychosocial function was assessed using Conners', teachers' and parents' rating scales. Psychological testing was performed to detect possible adverse effects of treatment. EEG recording including 24 hr ambulatory monitoring was used to

determine whether discharges were suppressed by treatment. In all but one patient the trial medication chosen was sodium valproate, and in two instances an increase in dosage of baseline valproate therapy.

During active treatment there was a reduction of discharge rate and an improvement in global rating of psychosocial function compared with baseline scores ($p< 0.05$ for both). Formal psychological testing showed no significant change attributable to adverse effects of medication. Unfortunately there were unavoidable confounding factors. All but one patient (who was seizure-free throughout) showed a reduction (mean 32.6%) of seizure frequency on active treatment. This was, of course, unexpected, as medication was already thought to have been optimised. Two children with improvement of psychosocial function during the active treatment phase showed only a minor reduction of interictal discharges in 24 hours telemetry. It was also impossible to exclude the possibility that improvement could be due to a psychotropic effect of sodium valproate. Such an effect has been postulated by Forsythe et al. (1991). The overall results were in accordance with the hypothesis to be tested, namely that subclinical discharges produce TCI, causing psychosocial dysfunction which can be ameliorated by the use of medication to suppress epileptiform EEG activity. However it was impossible to exclude the possibilities that the improvement noted was due either to improved seizure control or a direct effect of the medication. This is the first study to present such evidence under controlled conditions. It also highlights the problems likely to be encountered in such investigations and may serve as a guide to planning of future studies. A second issue is whether treatment of TCI, if desirable, is a practical possibility. Epileptiform EEG discharges are in general difficult to suppress by chronic AED administration. Drugs known to be effective in suppressing interictal discharges are sodium valproate, lamotrigine and benzodiazepines. The latter of course are known to produce cognitive deficits, which may offset any possible benefits of suppressing TCI.

1.5. Lamotrigine

1.5.1. Introduction

Lamotrigine, a triazine derivatinve (Fig. 1.18) is structurally and pharmacologically unrelated to other AEDs. It was initially synthesised as an antifolate agent, based on the hypothesis that folate has convulsive properties in animals and that some early antiepileptic drugs were considered to have an antifolate effect. However, it subsequently emerged that the very weak antifolate activity of lamotrigine was not responsible for its antiepileptic properties. It has a molecular weight of 256, a pK_a of 5.5 and relatively low water solubility: 0.17g/l in distilled water.

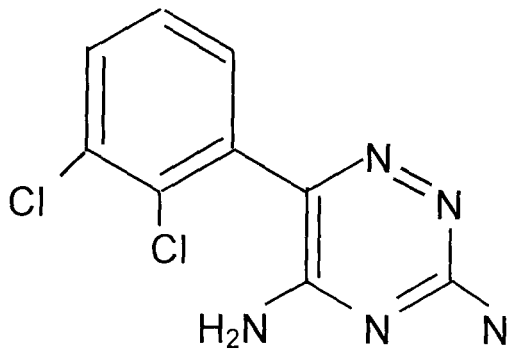


Figure 1.18: Structure of lamotrigine: 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine

1.5.2. Mode of Action

Antiepileptic drugs may suppress seizure activity by any or a combination of the following mechanisms:

- stabilisation of the neuronal membrane through direct effects on ion flux;
- enhancement of the effects of inhibitory neurotransmitters, e.g. GABA, either directly or via reduction of synaptic GABA transaminase;
- inhibition of excitatory neurotransmitters such as glutamate.

Preliminary studies in rats suggested that lamotrigine reduced veratrine-induced release of glutamate and, to a lesser extent, of aspartate in cortical slices (Leach et al.,

1986). However, lamotrigine did not act on the glutamate receptors themselves, but on presynaptic ion channels. Xie et al. (1995) showed that the drug is a use dependent inhibitor of voltage-gated Na+ currents, producing a marked reduction in normalised current with long stimulus duration (which stimulates epileptiform activity) but has minimal effect during short stimulation (Fig. 1.19).

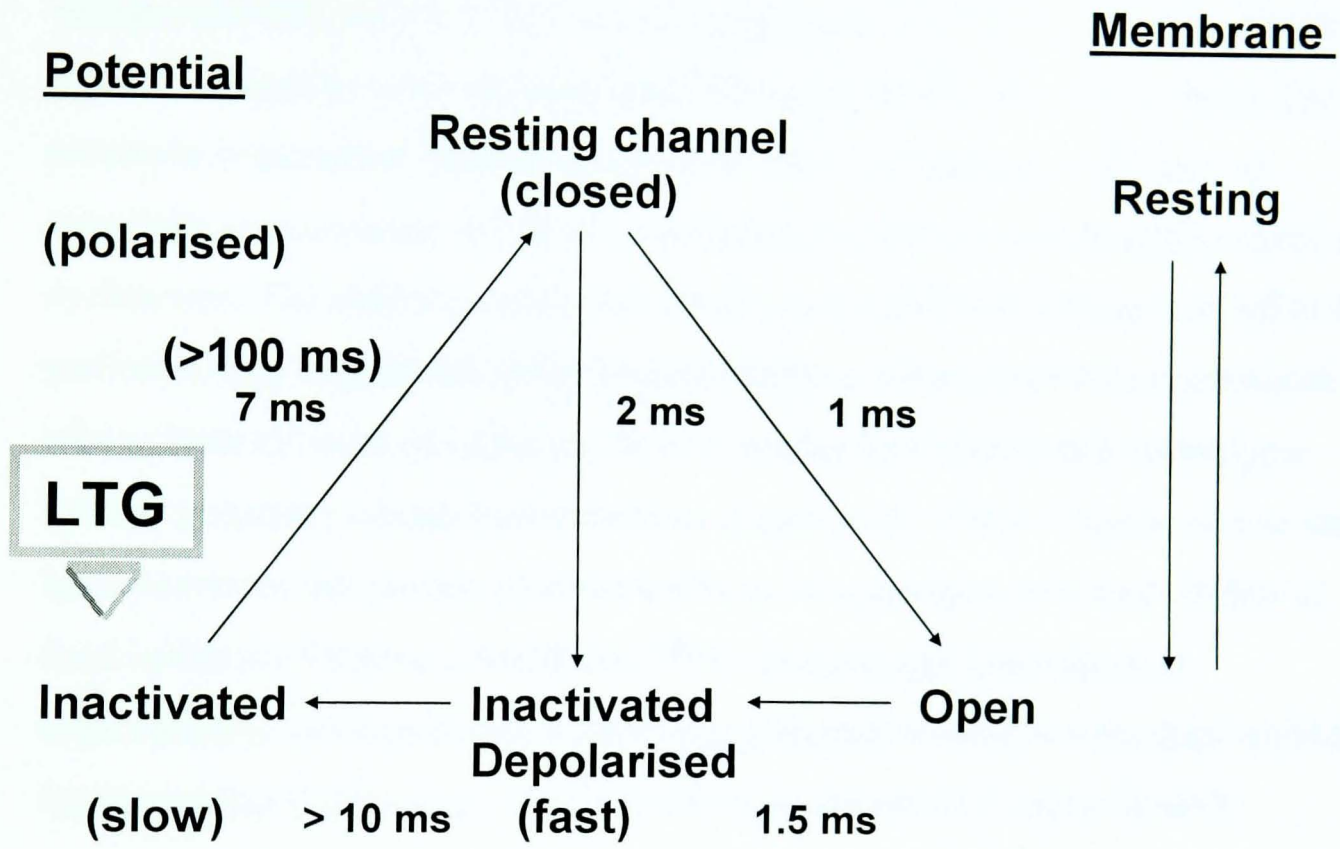


Figure 1.19: Mode of action. Lamotrigine blocks voltage dependent sodium ion channels of slow inactivation and thereby reduces excessive glutamate release in sustained rapid firing.

It had no effect on voltage-dependent activation or on fast inactivation, suggesting that lamotrigine acts on slow inactivation. Lamotrigine displays a use-dependent profile with the inhibition of Na^+ channels being more pronounced in rapidly firing neurons. Lamotrigine prolongs slow inactivation and thereby delaying opening of the Na^+ channels. Even at high concentrations (50 μmol/L), lamotrigine has been shown not to affect the pattern of Na^+ channel activity in normal neurones, nor to influence the EPSP-IPSP sequence. Therefore does not affect low frequency synaptic

transmission mediated through excitatory (i.e. glutamate) or inhibitory transmitters (i.e. GABA).

The affinity of lamotrigine for the inactivated state of the Na1 channel is about 0.012 mM (Xie et al., 1995), which compares favourably with effective clinical CNS concentrations of about 0.01– 0.03 mM (Leach et al., 1986).

In addition to its effect at the voltage-gated Na^+ channel, lamotrigine also inhibits voltage-operated calcium (Ca^{2+}) channels (Wang et al., 1996). Activation of both Na^+ and Ca^{2+} channels results in rising intracellular calcium levels and increased cellular metabolic requirement. Increased energy demand and cellular calcium levels contribute to excitotoxic cell death, a potential component of permanent cognitive dysfunction. The ability to reduce excitability in general, and calcium ion influx in particular, may explain the ability of lamotrigine to reduce cognitive impairment arising from episodes of ischemia. *In vitro* studies have shown that lamotrigine inhibits glutamate release from rat cortex (Leach et al., 1991), whereas *in vivo* studies have illustrated the cerebro-protective effects of lamotrigine in rodent models of focal ischemia (Smith and Meldrum, 1995). Interestingly lamotrigine is approximately twice as potent at inhibiting glutamate release *in vitro* than inhibiting GABA release (Leach et al., 1986). In contrast, phenytoin is approximately equipotent against the two neurotransmitters.

It is therefore argued that lamotrigine owes its antiepileptic properties to enhancement of slow inactivation, blocking prolonged rapid firing, as occurs in seizures, but has no effect on normal physiologic glutamate release at lower discharge rates. Lamotrigine thus appears to have a specific action against pathologic epileptogenic activity without interfering with normal brain function. Other drugs active at Na^+ channels, such as phenytoin and carbamazepine, have a similar effect that is both voltage and use-dependent, but phenytoin does not share the selective action of lamotrigine on the slow inactivated state (Kuo and Bean, 1994). Moreover, these drugs inhibit normal synaptic function, interacting with both NMDA and non-NMDA receptors (Hood et al., 1983; Griffith and Taylor, 1988).

1.5.3. Pharmacology

Lamotrigine exhibits linear pharmacokinetic features in adults over the dose range 50-400 mg. The drug is almost completely bioavailable, with a long half-life (24 hr) and linear kinetics (Cohen et al., 1987). The half-life of lamotrigine is increased in renal failure; this may be a consequence of inhibition of its metabolism by accumulation of the glucuronide. After oral intake, there is rapid absorption, with maximal concentration (C_{max}) occurring at 2 to 3 hours. After a single oral dose in normal subjects, peak concentration and area under the curve (AUC) are directly proportional to the lamotrigine dose in the range of 15 to 240 mg. The plasma elimination half-life ($t_{1/2}$) is 25-30 hr in drug-free volunteers. Time to C_{max} is increased after ingestion of food, but half-life and AUC are unaffected. Binding to plasma protein is about 55%. This is not apparently affected by the presence of co-medication (Miller et al., 1986). Lamotrigine does not affect drug-metabolising enzymes in the liver. Consequently, its potential for affecting the metabolism of other drugs is low. In patients taking hepatic drugs affecting the cytochrome P450, (phenobarbitone, phenytoin and carbamazepine) elimination of lamotrigine is increased ($t_{1/2}$ is reduced) (Binnie et al., 1986). Competitive inhibition of glucuronidation by valproate increases the half-life of lamotrigine (Binnie et al., 1986). Kinetic parameters for normal children are not available.

Autoinduction of lamotrigine metabolism is so low as to have no clinical significance. Lamotrigine does not materially affect the metabolism of other antiepileptic drugs, nor that of oral contraceptives (Holdic et al., 1991). An increased plasma concentration of carbamazepine-10,11-epoxide (CBZ-E) has been reported by some, but not confirmed by others (Binnie et al., 1987; Potter and Donnelly, 1998; Besag et al., 1998).

There appears to be true pharmacodynamic synergy between lamotrigine and valproate in typical absence seizures, West syndrome, and Lennox-Gastaut syndrome, i.e. an effect in excess of their kinetic interaction (Besag et al., 1995; Veggiotti et al., 1994). Lamotrigine appears to potentiate many unwanted effects of carbamazepine, like double vision or ataxia, in patients with carbamazepine levels in the upper therapeutic range. This appears not to be related to epoxide levels, although

the symptoms usually disappear if the dose of carbamazepine is reduced. There may also be a pharmacodynamic interaction responsible for the occurrence of tremor reported in patients taking lamotrigine and sodium valproate (Reutens et al., 1993).

1.5.4. Adverse Effects

The oral mean effective dose (ED_{50}) in mice and rats is in the range of 1.9-3.9 mg/kg, with corresponding plasma concentrations of the order of 1.5 μg/ml (Miller et al., 1986). The safety profile of lamotrigine in standard toxicological studies is excellent, the only problems described in animals is a cardiotoxic metabolite in dogs and accumulation in the kidney in white male rats. These were not found in humans.

As outlined above lamotrigine reduces glutamate release presynaptically, hence NMDA-activation is reduced. Non-competitive inhibitors of the NMDA receptor such as phebncyclidine (PCP) and MK801, induce short term memory loss and psychosis. In contrast, lamotrigine did not induce PCP-like central nervous system (CNS) effects (Leach et al., 1991) when given orally to rats at doses of 20 to 160 mg/kg. Preclinical single-dose studies showed that lamotrigine had less effect on ocular and manual tracking, peak saccadic velocity, and body sway than carbamazepine, phenytoin, or diazepam (Cohen et al., 1985; Hamilton et al., 1993).

In controlled add-on trials, central nervous system effects occurred more often on lamotrigine than on placebo. These included, in order of frequency, asthenia, diplopia, headache, somnolence, ataxia, dizziness, nausea, and nervousness. However, in a meta-analysis of the first four trials, none of these effects were statistically significant compared to placebo (Betts et al., 1991). In subsequent controlled and open studies, dose-related central nervous system side effects have been reported approximately in 10% of patients (Schapel et al., 1993).

The most common idiosyncratic reaction has been a drug rash, leading to withdrawal of some 2.3% of patients in open studies (Betts et al., 1991). This is usually a mild maculopapular eruption of delayed hypersensitivity type. Its incidence appears related to the initiation dose. It usually occurs within the first two to six weeks of administration and disappears rapidly when the drug is withdrawn. The rash is most

common in children, on monotherapy or when combined with sodium valproate, and is less frequent when the drug is combined with enzyme inducers. In comparative monotherapy studies, withdrawals because of rash were more frequent with carbamazepine than with lamotrigine (Brodie et al., 1995). Some patients have been successfully re-challenged starting on very low doses without recurrence of the rash (Besag et al., 2000). Rare serious events possibly associated with lamotrigine included Stevens-Johnson syndrome (0.11%), neutropenia (0.04%) and thrombocytopenia (0.03%). In controlled trials no adverse effect related to the weak antifolate action of lamotrigine has been detected.

Sudden unexplained death is a well documented complication of epilepsy, particularly in young adults with uncontrolled seizures. This risk is smaller for patients taking lamotrigine (Yuen, 1992). A few deaths have been recorded in patients taking lamotrigine following a rapid progressive illness with status epilepticus, disseminated intravascular coagulation and multiorgan failure. It is believed this was caused by the underlying status epilepticus rather then by lamotrigine as other cases with similar courses were independent of antiepileptic medication (Yuen, 1992).

Toxicity

There is no reported experience of deliberate overdosage with lamotrigine but some patients with lamotrigine concentrations of ≥ 15 μg/ml have reported sedation, ataxia, diplopia, nausea and vomiting.

Teratogenicity

Animal models sensitive to the teratogenic effects of valproate and carbamazepine offer no evidence of fetal malformations caused by lamotrigine. Currently, lamotrigine is not recommended for use by pregnant women.

1.5.5. Efficacy

As is usual, the second and early third phase studies were performed using lamotrigine as add-on therapy in adult patients with resistant partial and secondarily generalised seizures.

Increasing experience has indicated that the efficacy of lamotrigine is not limited to the restricted indications for which product licenses were first obtained. An analysis of pooled data of the first 677 adult patients entered into open clinical trials showed that a greater percentage of patients (mean, 32%) achieved a ≥50% seizure reduction than in the controlled studies (Binnie, 1994). It has become apparent that Lamotrigine is effective in partial, secondary generalised and primary generalised seizures in adults and children including atonic seizures and atypical absences (Fig. 1.20).

In addition to evaluating its effect on seizures, a number of studies have also examined the effect of lamotrigine on EEG activity. In one study five patients who had frequent interictal discharges had a reduction of 78 - 98% in discharge rate following a single oral dose of 120 mg or 240 mg lamotrigine. Six patients with photosensitivity showed a marked reduction in response to photic stimulation (Binnie et al., 1986). Another study involved a double-blind, cross-over design with placebo, oral diazepam, lamotrigine 120 mg or 240 mg in six patients. Both treatments significantly reduced interictal spikes as compared with placebo, but lamotrigine was less effective than diazepam (Jawad et al., 1986). These findings have been confirmed by others (Chevalier et al., 1995; Marciani et al., 1995). In a recent study on the effects of lamotrigine on nocturnal sleep, daytime somnolence and cognitive functions in 13 adults with drug-resistant focal epilepsy a significant reduction of discharges was found from baseline (Placidi et al., 2000). Using a ambulatory spike and wave monitor Besag (1995) evaluated the effect of lamotrigine on spike and wave discharges in 17 children and adolescents with epilepsy. There was a reduction of discharges of more than 80% compared with baseline in 8 patients. This was not always correlated with a reduction of overt seizures. Eriksson and colleagues (2001) described a significant reduction of duration of discharges in 12 patients with Lennox-Gastaut syndrome. Longer discharges (>30 sec) were more likely to be suppressed than shorter discharges.

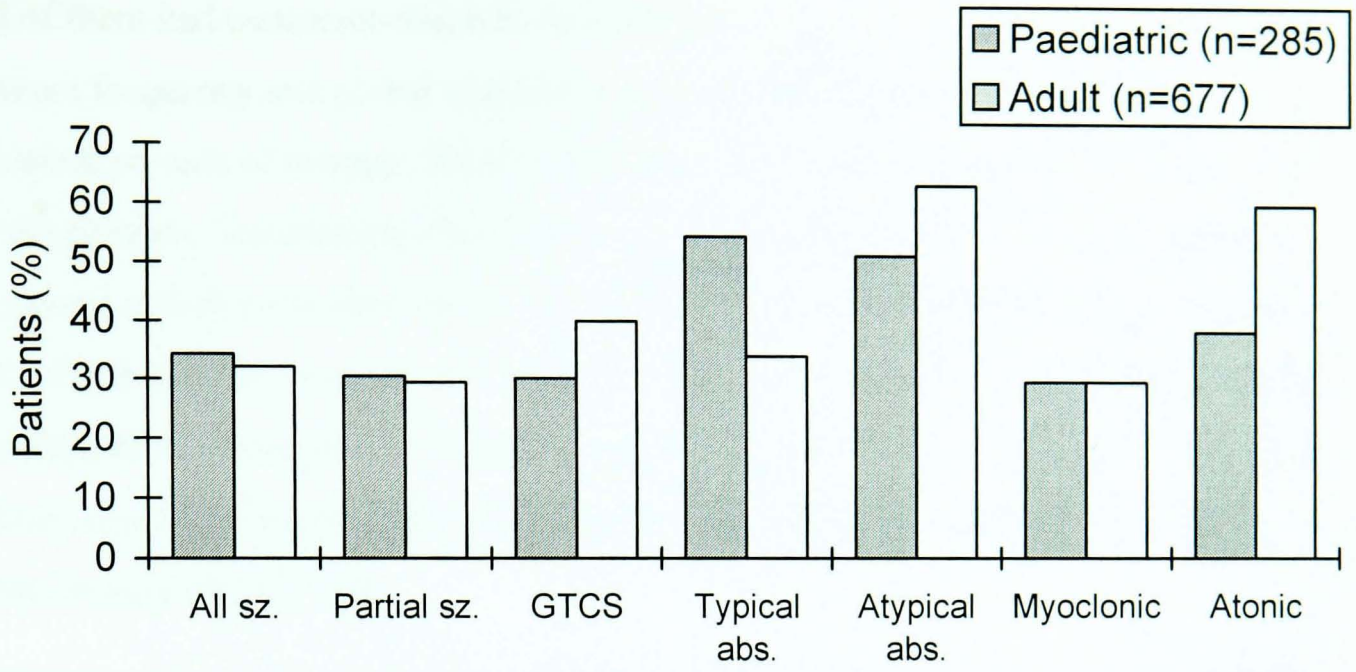


Figure 1.20: Efficacy of lamotrigine in children and adults. Patients with 50% reduction of seizure frequency over 12 week treatment with lamotrigine. (after Binnie, 1994 and Besag et al., 1995)
Sz: seizures, GTCS: Generalised tonic-clonic seizures.

First monotherapy studies comparing lamotrigine and carbamazepine or lamotrigine and phenytoin showed no difference in the efficacy between the drugs for partial seizures with or without secondary generalisation and for primary generalised seizures (Brodie, 1996). One-hundred and fifty-one patients with newly diagnosed epilepsy in eight UK centres completed a 48-week randomised, double-blind, parallel-group trial (Brodie et al., 1995). The proportion of patients maintained seizure free during at least 24 weeks of treatment was almost the same in patients receiving lamotrigine (39%) or carbamazepine (38%). Overall fewer patients on lamotrigine than on carbamazepine withdrew because of adverse events.

1.5.6. Use in Children

Pooled data from five multicenter, open-label add-on studies with similar protocols were analysed to assess the efficiency and tolerability of lamotrigine in children (Besag et al., 1995). A total of 285 children under the age of 13 years were included.

All of them had treatment-resistant epilepsy and most had two or more seizure types. Seizure frequency and global evaluation were assessed at the end of four successive 12-week periods of therapy. Seizure frequency was reduced by 50% or more in 34% of the patients. Lamotrigine was effective in all seizure types examined, particularly in typical and atypical absence seizures (Fig. 1.20). Atonic seizures also responded well. Improvement was well maintained during the treatment period. The commonest reported side effects were somnolence (16.8%), rash (16.5%), vomiting (12.3%) and seizure exacerbation (11.6%). Adverse experience led to withdrawal of treatment from 36 patients (12.6%).

Particular efficacy has been claimed in the Lennox-Gastaut syndrome, most notably by Timmings and Richens (1992), where 10 of 11 patients achieved a ≥50% seizure reduction. Chevalier et al. (1995) reported 85-95% seizure reduction in 10 of 16 patients with Lennox-Gastaut syndrome, and 70-90% reduction in EEG discharges during 24-hour monitoring. Similar efficacy has been described in a double-blind, placebo controlled crossover study in 27 children and young adults with drug-resistant epilepsy, mostly Lennox-Gastaut syndrome (Eriksson et al., 1998).

Reports of its use in infantile spasms (West's syndrome) are as yet inconclusive. In one study lamotrigine was combined with sodium valproate and 5 of 30 patients become and remained seizure-free (Veggiotti et al., 1994).

Adverse experiences in children are similar in nature and incidence to those in adults (Table 1.2). Drug rash has been commoner than in adults (16.5% in pooled data - Besag et al., 1995). This may partially reflect the fact that the largest paediatric trial used a dose escalation more rapid than that now recommended.

Table 1.3 shows the recommended regimens for administration of lamotrigine in adults and children.

	Incidence (%)	
Adverse events	paediatric (n=285)	adult (n=677)
Somnolence	16.8	17
Rash	16.5	6.4
Vomiting	12.3	6.2
Aggravated reactions	11.6	2.5
Ataxia	6.0	14.3
Headache	6.0	13.1
Hyperkinesia	5.6	0.3

Table 1.2: Adverse events of lamotrigine reported in pooled paediatric and adult populations in open-label add-on studies.

	Children, mg/kg daily			Adults and children > 12 y, mg daily		
Co-medication	Enzyme inducers	None	VPA*	Enzyme inducers	None	VPA*
1st 2 weeks	2	0.5	0.2	50	25	12.5
2nd 2 weeks	5	1	0.5	100	50	50
Maintenance	5-15	2-10	1-5	200-400	100-200	100-200

* in mono- or combination therapy, VPA: Sodium Valproate

Table 1.3: Regimens for administration of lamotrigine [in mg].

1.5.7. Effects on cognitive function and behaviour

A number of open and controlled studies have shown that lamotrigine is less likely to produce cognitive deficits commonly associated with AED. Additionally, when lamotrigine is used as an add-on therapy, any pre-existing cognitive problems are not exacerbated and in some cases are clearly improved (Buchanan, 1995).

Animal studies

Animal studies have shown not only that lamotrigine has minimal CNS depressant effects (see above), but also that it may have positive effect on cognitive function. Mechanisms of cognition and memory are poorly understood at the molecular level. However, long-term potentiation is a form of synaptic plasticity that may form a basic mechanism for memory and learning (Bliss and Collingridge, 1993). Two recent studies (Xiong and Stringer 1997; Otsuki et al., 1998) reported that at anticonvulsant doses, lamotrigine had no effect on either the induction or the maintenance of long-term potentiation. In the gerbil, temporary bilateral occlusion of the common carotid arteries impairs escape from the Morris water maze and subsequent histological examinations reveal severe deterioration of hippocampal neurons (Wiard et al., 1995). Gerbils pre-treated with lamotrigine are significantly better at escaping from the water maze and have significantly less ischemic cerebral injury. In developing rats, repeated administration of lamotrigine did not impair performance (bar holding test and rotorod test) and spontaneous behaviour (open field test) compared to control siblings (Mikulecka et al., 2004).

Taken together the existing preclinical data suggest that lamotrigine treatment does not result in any cognitive impairment and can protect against excitotoxic and ischemic insults.

Normal volunteers

Volunteer studies have the advantage of fewer confounding factors thereby providing an early insight into the cognitive effects of an AED. A number of volunteer studies have been conducted that indicate that acute administration of lamotrigine is not associated with cognitive impairment (Cohen et al., 1985; Hamilton et al., 1993). In five normal subjects and five patients with age-associated memory impairment, lamotrigine improved immediate and delayed visual memory. Curiously, list learning and finger tapping were impaired, whereas digit symbol, similarities, digit span, Corsi and Stroop test were unaffected. Five volunteers received lamotrigine (initial dose 3.5 mg/kg, then titrated to a maximum of 7.1 mg/kg) in a single-blind manner and were assessed for change in cognitive function after 2 and 4 weeks (Martin et al., 1999). There was no significant change in any of the neurocognitive measures relative to baseline performance. The effects of lamotrigine and carbamazepine were compared in 23 volunteers in a 10-week, cross-over study (Meador et al., 2001). The neuropsychological battery in this study consisted of 19 instruments yielding 40 variables including both subjective and objective measures. Lamotrigine was associated with better performance or fewer side effects in 17 of the variables, while there were no statistical differences seen in the remaining variables. The authors concluded that lamotrigine produces significantly fewer unwanted cognitive and behavioural effects than carbamazepine. A recent study with parallel design by Aldenkamp and co-workers in 30 volunteers showed evidence for a selective effect of cognition in one out of 12 measures, relative both to placebo and to valproate (Aldenkamp et al., 2002). However, this study has been criticised by other (Dodrill, 2002).

Although these studies support the favourable cognitive profile of lamotrigine, data from healthy volunteers should be treated with caution. The drug exposure periods are usually short and the dose smaller than in clinical practise. Furthermore, the number of subjects is usually very small. It is possible that chronic treatment results in different types of cognitive impairment that cannot be observed during short-term treatment.

Patients with epilepsy

In patients with epilepsy open clinical studies and controlled studies have found few or no cognitive side effects compared to other AED or placebo.

A double-blind, randomized cross-over study in adult patients with epilepsy has reported no significant effect on cognitive function of lamotrigine compared with placebo when used as adjunctive therapy (Banks et al., 1991). Similar results were reported by others (Smith et al., 1993; Placidi et al., 2000).

In one controlled study with patients with newly diagnosed epilepsy the effects of lamotrigine on cognitive functioning have been compared with those of carbamazepine (Brodie et al., 1999). Patients completed tests consisting of verbal learning and memory tests (Verbal Learning I and II, Delayed Recall, and Recognition) and attention and mental flexibility (Semantic Processing I and II, Trail Making test, Logical Reasoning and Stroop Test) at baseline and then periodically for up to 48 weeks. Significant differences favouring lamotrigine over carbamazepine were observed with Semantic Processing, Verbal Learning, and Stroop Test. The authors concluded that lamotrigine may have a favourable long-term effect on cognitive function when compared with carbamazepine.

Several uncontrolled studies reported improved concentration, verbal and non-verbal communication, school or work performance, and behaviour, particularly in children with learning difficulties (Gibbs et al., 1992; Uldall et al., 1993; Fowler et al, 1994; Uvebrant and Beuziene, 1994; Buchanan, 1995). In 50 children with intractable epilepsy, 21 showed a reduction in absence and complex partial seizures and 5 of these became seizure-free (Uvebrant and Beuziene, 1994). After lamotrigine was added to existing therapy, parents of 24 of these children reported an improvement in their children's "mental state," including longer attention span, improved alertness, and emotional stability. Eight of thirteen autistic children in this study showed reduced symptoms after the addition of lamotrigine therapy. This improvement was apparently unrelated to seizure control.

Conflicting results have been reported by Ettinger and colleagues (1998): seven patients with epilepsy and mental retardation lamotrigine add-on caused both positive and negative psychotropic effects. These findings were based on the observations of

parents and supervising staff. Positive effects included reduced irritability and more compliance with simple instructions; negative effects included behavioural deterioration with temper tantrums, restlessness, and hyperactivity.

Aggressive behaviour has been associated with lamotrigine, particularly in children with learning difficulties (Besag et al., 1995; Beran and Gibson, 1998). In the above mentioned multicenter study (Besag et al., 1995) 2.5% of children were found to have behavioural side effects. The authors questioned however, whether this could at least partially be attributed to patients becoming more alert, active, and demanding (Besag et al., 1995, Besag, 2004). This is arguably not an adverse effect but a necessary stage in the rehabilitation of such patients following improved seizure control.

Quality of Life

A number of patient assessment questionnaires exist to test the impact of epilepsy and AED treatment on quality of life.

In a placebo-controlled add-on study, patients with difficult-to-treat epilepsy were assessed with the Health Related Quality of Life inventory and a small cognitive test battery. They found a significant improvement of scores on happiness and mastery in a quality-of-life study during active treatment (Smith et al., 1993). This improvement was considered to be independent of seizure control.

The Side Effect and Life Satisfaction (SEALS) inventory is a patient-completed questionnaire containing five categories: Cognition, Dysphoria, Temper, Tiredness, and Worry. It has been developed to evaluate the effect of epilepsy and AED treatment on cognition and affect (Gillham et al., 1996; Gillham et al., 2000). It was validated in a large study comprising 923 patients, 256 of whom were newly diagnosed with epilepsy (Gillham et al., 1996). The trials compared the short-term effect of lamotrigine with carbamazepine on seizure frequency and quality-of-life. It was found that patients receiving lamotrigine showed a greater improvement in the SEALS, over four weeks of treatment, than patients taking carbamazepine. Randomized controlled clinical trials have further indicated the positive impact of

lamotrigine on aspects of quality of life. In a recent comparative study, lamotrigine and phenytoin were similarly effective in seizure control in a group of newly diagnosed patients with untreated partial or generalized tonic–clonic seizures. However, significant differences between the two AEDs were observed on quality-of-life measures (Steiner et al., 1999). Treatment with lamotrigine resulted in a reduction in mean total SEALS scores, indicating an improvement in aspects of health-related quality of life. Conversely a slight increase in SEALS scores was recorded in the PHT group. The authors concluded that lamotrigine displayed a lower incidence of central nervous system side effects when compared with phenytoin (Steiner et al., 1999). Similar results were found in another large randomised study comparing lamotrigine with carbamazepine in newly diagnosed patients evaluated with SEALS. Dosages were adjusted according to efficacy, adverse events and plasma concentrations, the median daily doses being lamotrigine 150mg or carbamazepine 600mg (Brodie et al., 1995). Patients were evaluated at baseline and after 4, 12, 24 and 48 weeks of treatment. 133 patients completed the study (73 lamotrigine, 60 carbamazepine). The cognition subscale as well as other subscales showed improvements in the lamotrigine group at 48 weeks compared to baseline. In contrast, deterioration in the cognitive subscale was seen in the patients randomised to carbamazepine.

Mood

A related issue is the effect of lamotrigine on mood. Ketter et al. (1999) divide the mood and affect profiles of antiepileptic drugs into two separate classes: The first class cause sedation and are used for their anxiolytic and antimanic effects, e.g., for the treatment of agitation and aggression. These effects are assumed to be related to the enhanced of GABA-mediated inhibition. Benzodiazepines, barbiturates, and sodium valproate belong to this class of drugs. The major CNS side effects are fatigue and cognitive slowing. The second class has an opposite, i.e., activating effect, associated with increased glutamate excitatory neurotransmission. This class of drugs is used for its anergic profiles, e.g., for the treatment of depression, apathy, and hypersomnia. Their assumed effect is cognitive activation. Lamotrigine belongs

to this class of drugs (Ketter et al., 1999; Reijs et al., 2004). The major side effects are hyperactivity, hyperirritability, and possibly insomnia. In psychiatry, lamotrigine is used for the treatment of depression (Ketter et al., 1999). Mood improvements have been reported in several open clinical studies in epilepsy patients (Smith et al., 1993; Brodie et al., 1995; Schapel and Chadwick 1996; Besag 2000). In a controlled trial of interictal depression, lamotrigine monotherapy was associated with earlier and greater improvement compared with valproate monotherapy (Edwards et al., 2001). Recently it has been suggested that lamotrigine also has a broad spectrum efficacy in bipolar disorder (Calabrese et al., 1998). In a controlled study it was well-tolerated and had a similar effect to lithium, particularly for prophylaxis of depression (Calabrese et al., 2003). The reported effects on quality of life and behaviour may be partially related to and explained by these mood effects.

It remains however unclear whether the improvement of psychosocial function is due to suppression of interictal discharges or due to an independent psychotropic effect (Besag, 1995; Binnie, 1994).

Chapter 2: Aims of the study

The aims of this study were

1. to examine factors influencing the incidence of interictal EEG discharges in children with well-controlled epilepsy (chapter 4);
2. to measure effect of lamotrigine on of interictal EEG discharges in children with well-controlled epilepsy (chapter 5);
3. to measure effect of lamotrigine on behaviour in children with well-controlled epilepsy (chapter 6);
4. to measure effect of lamotrigine on cognition in children with well-controlled epilepsy (chapter 7);
5. to measure effect of interictal EEG discharges on behaviour and cognition in children with well-controlled epilepsy (chapter 8).

Chapter 3: Methods

Many aspects of cognitive and behavioural tests, patient recruitment and analysis were common to most parts of the research. To avoid repetition, they are described in this section, and referred to in subsequent chapters. Methods specific to each study are included in the relevant chapters.

3.1. Methodological Principles of Testing Neuropsychological Functions

3.1.1. Intelligence Tests

An intelligence test provides a general assessment of the child's development or intellectual status. It is the first stage in evaluating the child's cognitive function and may be used as an initial background against which to interpret other test performance and reported behavioural and educational problems.

The most common test used for school children is the WISC-R III (Wechsler Intelligence Scale for children-Revised version). It originated from the WISC (Wechsler, 1949), a downward extension of adult intelligence scales and was designed for the age range of 6 years to 16 years and 11 months. The test consists of 12 subtests divided equally into verbal and performance scales. The verbal scale is comprised of Information, Similarities, Arithmetic, Vocabulary, Comprehension and Digit Span subtests and the performance scale includes the Picture Completion, Picture Arrangement, Block Design, Object Assembly, Coding, and Maze subtests. A short version of the test includes the subtests Similarities, Vocabulary, Comprehension, Block Design and Object Assembly. As there is a clear learning

effect the test should not be repeated before 12 months. Administration time of the full test lasts approximately 60 to 90 minutes; for the short version 40 to 60 minutes.

The instrument was constructed from the premise that intelligence may be defined as an individual's capacity to understand and cope with the world (Wechsler, 1974). The author emphasises that this definition requires an assessment instrument that appreciates the global nature of intelligence and avoids placing undue emphasis on any one ability in assessing overall intellectual capacity. The subtest tasks therefore attempt to identify specific areas of delayed development or cognitive impairment. If specific discrepancies are very marked the full IQ may not give an accurate picture of the child.

The tests generate standardised scores for Full Scale (FIQ), verbal (VIQ), and performance IQ (PIQ), individual subtests-scaled scores, and test-age equivalents.

The psychometric properties of the WISC-R have been extensively researched. Outstanding reliability is reported, with consistently strong internal consistency reliability coefficients (Wechsler, 1974).

In this study the short version of the WISC-R III were performed by all children at baseline to assess their overall intellectual abilities and mental age. IQ testing was performed while the child was wearing the ambulatory EEG recorder whenever possible in order to correlate performance with the occurrence of subclinical epileptiform discharges.

3.1.2. Computerised neuro-psychological test-battery

In order to test the effects of drugs on cognition a number of functions have to be tested. This is not only because a drug may affect one or several functions but also because there are individual responses in different patients.

The FePsy test battery (Fe = iron, psy = psychological) is a computerised neuro-psychological test battery. The development started by Binnie and co-workers in the

1970s with the development of memory tests with simultaneous EEG registration (Aarts et al., 1984). Subsequently a cognitive test battery has been built up to (1) assess cognitive function in patients with epilepsy; (2) measure cognitive side effects of antiepileptic drugs; (3) measure effects of subclinical epileptiform discharges; and (4) used preoperatively during assessment for Neurosurgery (Aldenkamp et al., 1987; Aldenkamp et al., 1990). The battery includes parallel test versions in which stimuli are selected randomly from a larger pool, tests which are sensitive to subtle changes and the option for simultaneous registration of the EEG. Results are stored in a database and can be passed to an ASCII file for subsequent analysis. For this study two subtests of this battery were used, a recognition memory test and the computerised visual searching task for repeated testing.

The following cognitive domains have been established as being particularly vulnerable in patients with epilepsy: speed of information processing, memory, alertness, sustained and focused attention, and motor fluency. Some studies also mention language and problem solving (Aldenkamp et al., 1987, 1990). The battery used in this study covers all of these domains, with particular emphasis on memory.

Continuous Performance Test (Tracker test)

The tracker test is a computerised test of sustained attention and vigilance. A small white square is seen on the touch screen. The patient has to keep a finger pressed on the white square whilst it moves randomly around the screen. The square stays white whilst a finger is on it, and becomes orange when it is off (Figure 3.1). There are three parts to the test but only the Adaptive Touching Task was used. The variable of interest was the difficulty level achieved (speed of 1-20), based on achieving more than 40% of the time on target. It was performed without EEG co-registration.

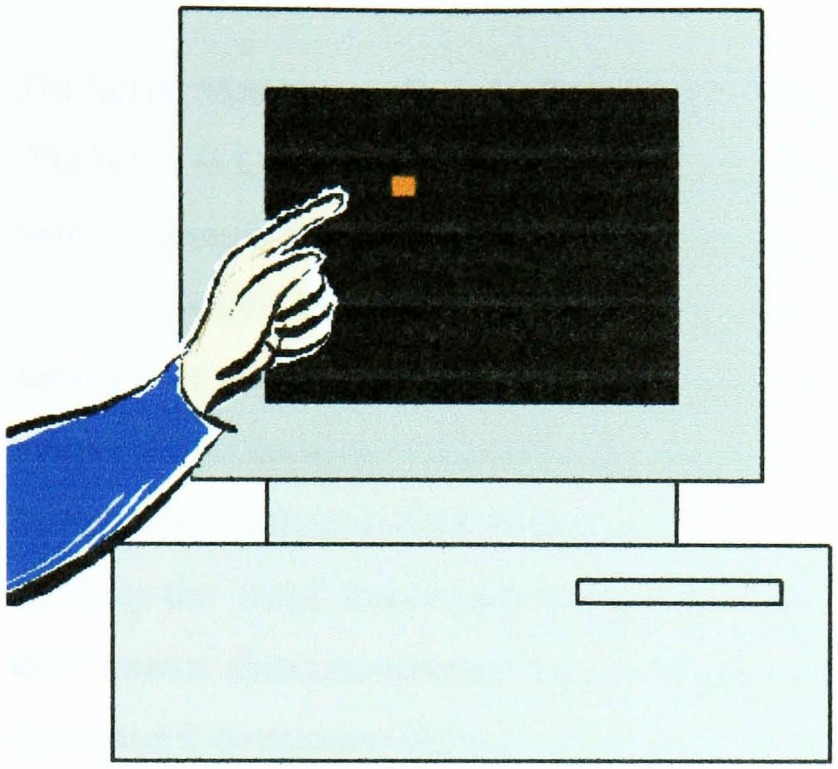


Figure 3.1: Continuous performance test: A little white square is seen on the touch screen. The patient has to keep a finger pressed on the white square whilst it moves randomly around. The square turns orange when the finger is no longer on it.

Verbal and Non-verbal Recognition Test

These computerised memory test exists in a simultaneous and a serial form. In this study only the simultaneous form was used. In the verbal version a pre-set number of 4-letter words are presented (learning phase) with a presentation time of 1 second per item. After a delay of 2 seconds, the screen display changes to show one of these words with distractors. This target item then has to be identified. In the non-verbal version abstract figures are used instead of words. The degree of difficulty can be varied, e.g. the memory set can consist out of 2, 4 or 6 words and out of 3 or 4 figures. The number of items used were be decided before the first test according to the results of the WISC-R III and a short reading test, then staying the same throughout the study. Both number of correct responses and the length of time over which the test is performed were recorded.

Serial Matching to Sample Tests (SMTS-16)

The Serial Matching to Sample Tests SMTS-16 has been developed by Coleshill (PhD by S.G.Coleshill,1999). It is a computerised YES-NO delayed recognition test with a 1 minute distractor interval which samples recognition memory across a range of 1 - 3 minutes. There are two versions: 'Words' and 'Faces', which have been shown to be sensitive to hemispherically lateralised cognitive deficits in patients with temporal lobe epilepsy (Coleshill et al., 2004). Both versions are composed of two subtests with different items. In each subtest the patient is shown 8 items (either words in the 'word' test or faces in the 'face' test) at the start of the test followed by the 1 minute distractor interval. Sixteen words or faces then appear individually (8 items and 8 distractors) and the patient tries to determine whether each appeared in the group at the start of the test (Figure 3.2).

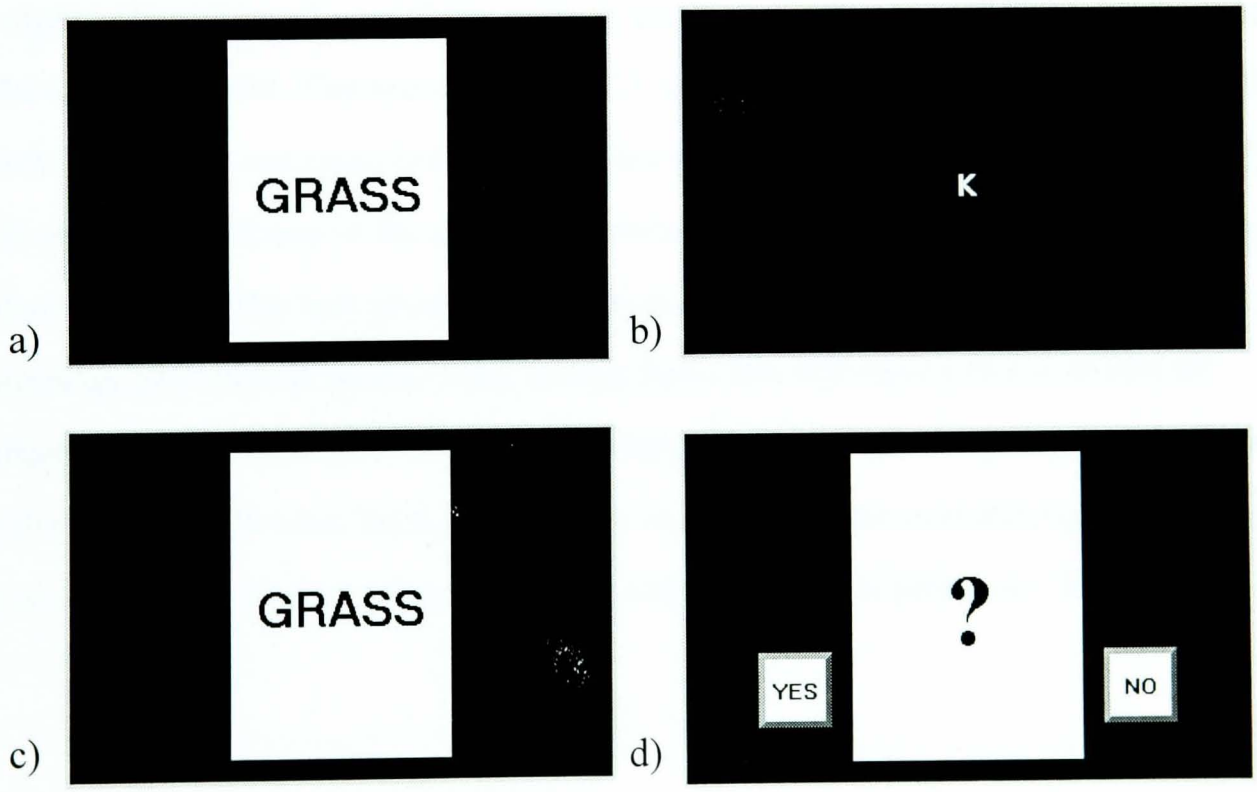


Figure 3.2: Serial Matching to Sample Tests SMTS-16 'Words': a) presentation of a series of items (here words), followed by a one min distractor interval (patient has to call out letters a and b). In the recognition phase the patient is presented with a series of 16 words and d) has to determine whether he has seen this item before or not.

Each subtest comprises of 16 stimuli (8 targets and 8 distractors). The main outcome measure of the tests is the number of words correctly identified as having appeared before minus the number of words incorrectly identified as having appeared before (discrimination score). The tests also measures bias to one response (yes or no). If there is no response bias then C=0, maximum bias values range from -2.5 (liberal) to +2.5 (conservative).

Computerised Visual Searching Task

This test has been adapted from the Goldstein's visual searching task. It discriminates successfully between brain damaged individuals, normal and psychiatric patients. The task consists of finding a centred grid pattern out of 10 surrounding patterns, only one of which is identical (Figure 3.3). Grid patterns are displayed in a checkerboard fashion and are numbered from 1 to 10. In a second version for older children 24 pattern are presented. The central target pattern is denoted by an arrow on the right side and is selected from each of the four quadrants to balance the location of the matching grid. The test consists of 20 trials (the 10 patterns change after 10 trials). Responses are recorded by typing the correct number from the keyboard. The main outcome measure is the median response time in milliseconds, but the error rate is also collected. The test gives an indication of the accuracy of information processing and mental speed. Time scores from this test have proven useful in evaluating cognitive effects of anticonvulsants in patients with epilepsy. A marked age dependent effect has been found, with control subjects performing over twice as fast at 18 years of age as at 8 years of age (Alphers and Aldenkamp, 1990).

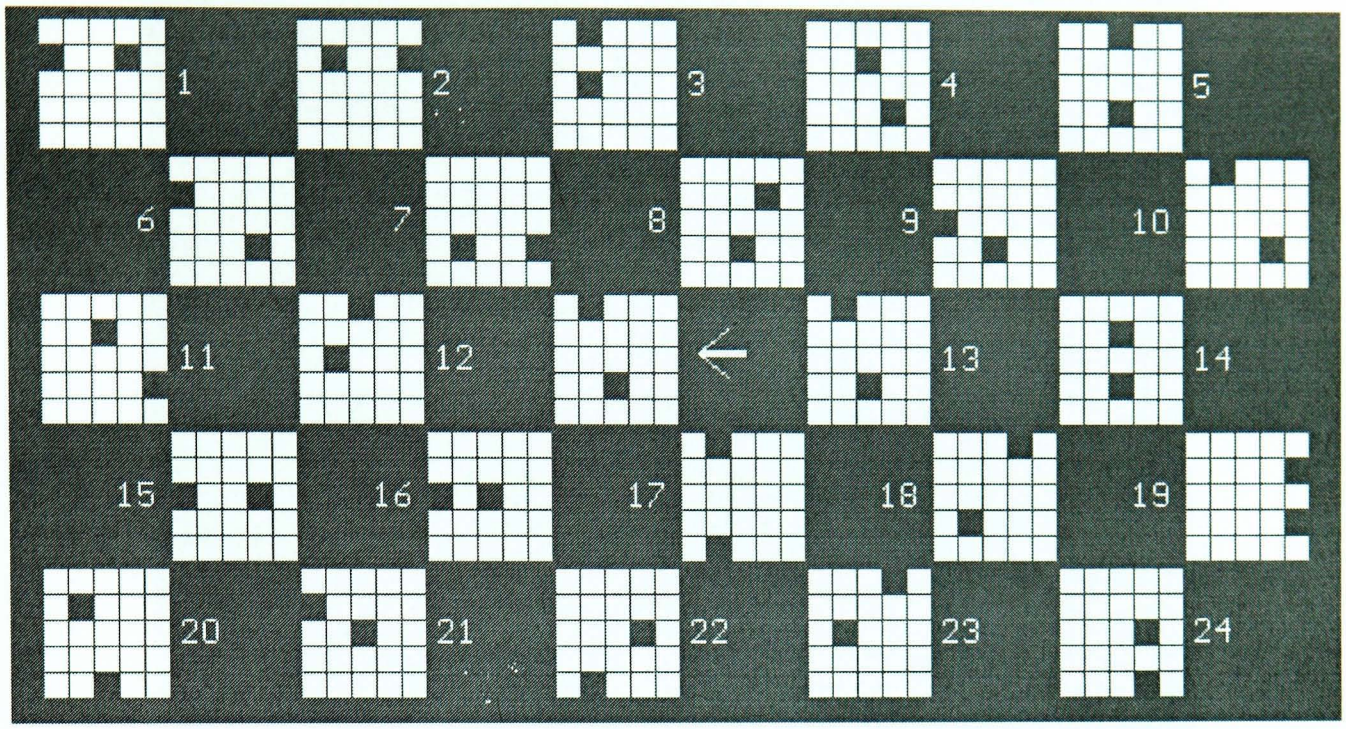


Figure 3.3: CVST: twenty-four numbered grid patterns are displayed in a checkerboard fashion. The central target pattern is denoted by an arrow on the right side and the patient has to find the matching grid (here number 13).

Binary Choice Reaction Time Test (Tiger Test)

The 'Tiger test' is a computerised binary choice reaction time task. In this task a tiger's head is shown on the left or right hand side of the computer screen (Figure 3.4) and the patient has to respond as quickly as possible by pressing either the '\' & '/' keys on the keyboard with the corresponding left or right hand. The speed of presentation is self-paced, a response is instantly followed by substitution of another block in either the same or the opposite position. Thirty tiger stimuli are presented each side, with positions pseudo-randomised, so that the stimulus is not presented consecutively on one side more than three times. The median reaction speed and accuracy for each hand will be recorded. By introducing a decision component (right or left) the reaction time reflects not only motor speed but also the decision making process.

Figure 3.4: Tiger test (binary choice reaction time test): stimulus presentation on the left side'\'key has to be pressed.

3.2. Methodological Principals of Behavioural Measurements

3.2.1. Conner's Parent and Teacher Rating Scales

Children with epilepsy may suffer from a number of problems which affect their behaviour and learning. The Conners' Parent and Teacher Rating Scales were developed to characterise patterns of children's behaviour. They are derived from two questionnaires, one completed by parents and one by teachers (Conners, 1989). They are relatively brief instruments standardised on the normal population. Both exist in a short version (often used as a clinical instrument to assess hyperactivity) and a long version, mainly used in research to assess hyperactivity and other behavioural abnormalities. They have been used in numerous investigations of children with epilepsy over the last 15 years (Cull et al., 1996; Ferrie et al., 1996; Aman et al., 1992; Stores, 1978).

The Conners Teacher Rating Scale (CTRS) has either 28 or 39 items. In this study the 39 item questionnaire was used. It includes six subscales labeled as I) anxious-passive, II) asocial, III) conduct problem, IV) daydream-attention, V) emotional-indulgence and VI) hyperactivity. Each item is rated with one of four responses: not at all (code 0), just a little (code 1), pretty much (code 2) or very much (code 3) and is rated depending upon the degree to which the behaviour is present in the patient during the preceding month. It was standardised on normal Canadian children aged 4 to 14 years (Conner et al., 1989). Normative data are available separately for groups formed by age and gender. The scales are factor analytically derived scales for assessing problem behavior in children. Raw scores are translated into T-scores by sex and age. The T-scores have a mean of 50, a standard deviation of 10 and higher scores denote more serious behavior problems.

The teachers' scale allows assessment of the child over a period in different situations by comparison with a normal range. In school the child is confronted with age appropriate tasks and experiences and must function in a complex social system posing many problems of adaptation that teachers are accustomed to observing.

The Conners' Parent Rating Scale (CPRS) has either 48 or 93 items In this study the 93 item questionnaire was used (appendix b). The parents' rating scale includes eight subscales designated as I) antisocial, II) anxious-shy, III) conduct disorder, IV) hyperactive-immature, V) learning problem, VI) obsessive-compulsive, VII) psychosomatic and VIII) restless-disorganized. As for the CTRS, each item is rated with one of four responses; not at all, (code 1), just a little (code 2), pretty much (code 3) or very much (code 4). Normative data for the CPRS 93 are based on a sample of normal children aged 6 to 14 years.

Test-retest reliability coefficients for the CTRS-39 range from 0.72 to 0.91 over 1 month (Conner, 1969). Over a year the reliability remains at a moderate level, ranging from 0.33 - 0.55 (Glow et al., 1982). The reliability of the CPRS-93 over one year ranges from 0.40 for the psychosomatic scale to 0.70 for the hyperactive-immature subscale (Glow et al., 1982). Inter-rater reliability has been assessed in abnormal groups only and is reported to be between 0.46 and 0.94 for different

domains (Conner, 1989). Although acceptable, parent-teacher correlation's tend to be slightly lower than mother-father and teacher-teacher correlation's. Additionally, mothers' ratings of their children's behaviour have been shown to correlate significantly with teachers ratings, whereas fathers' ratings do not (Schaughency and Lahey, 1985). Internal consistency as assessed by the alpha reliability coefficients vary from 0.61 - 0.94 for the CTRS-39. There are no similar published data for the CPRS-93.

3.2.2. Statistical analysis

The distribution of the between patients variability for the composite Connor's rating scale score has a standard deviation of approximately 5 units with a mean 50. 128 patients would be required for a parallel group study, to be able to detect a change in the composite score of 2.5 units, with 80% power and a 2-sided test at 5% significance. For a crossover study design, the between patient variability is removed, and an estimate of the within patient variability would be required. This is not available in this patient population, although, it can be assumed that a smaller number of patients would be required than for a parallel group study. It was considered that 60 or more patients, randomised equally between the two treatment groups should suffice to enable this study to achieve its objectives.

Composite scores were calculated from the teacher's version and the parent's versions of the Connor's Rating Scale by finding the mean score of each of the sub-scales for the parents' and teachers' scale separately, and then taking an unweighted mean of the two resulting means. Missing values were accounted for by adjusting the denominator in the individual sub-scale mean calculations. It was assumed that the composite score were approximately normally distributed.

3.3. Methodological Principles of TCI Testing

3.3.1. Requirement of TCI Tests

The computerized neuropsychological TCI tests described here were developed by Steven Coleshill (S.G. Coleshill, PhD 1999) and are used by the Department of Clinical Neurophysiology at King's College Hospital, London in the clinical assessment of the cognitive effects of subclinical EEG discharges. In addition to this study they are currently employed in a series of studies at King's College Hospital, on the effect of stimulation-induced epileptiform discharges and of the cognitive effects of both temporal lobectomy and vagus nerve stimulation.

The primary purpose of the test is to enable continuous cognitive testing with simultaneous EEG recordings, so that the effects of small fluctuations in cognition can be correlated in real time with EEG changes.

According to Aarts et al. (1984) a routine test for TCI should fulfil the following criteria: (1) The task must not so suppress epileptiform activity so that testing is impossible (see section 1.3.5). (2) The test must be acceptable for administration over a period sufficiently long for the effect, if any, of an adequate number of discharges to be observed. In practice, patients must generally be willing to perform the task for at least half an hour. (3) The difficulty must be adaptable to the patient's level of performance. Easy tasks are relatively insensitive to TCI, but increasing task difficulty may either decrease or increase the amount of epileptiform activity. (4) The task must test cognitive activity continuously. If it is intermittent, discharges may fall in the intervals between trials. (5) The test should have face validity. The clinical relevance is more obvious if the cognitive impairment demonstrated is of practical relevance, as for instance impaired verbal memory in a school child or increased reaction time in a motorist. (6) The test should differentiate between different psychological functions and between different regions of the brain.

As TCI testing is using a within-subjects methodology it is crucial to ensure equivalence of stimulus items used in each test. In order to demonstrate that there is a difference between cognitive performance with and without EEG discharges, the

variability in the pool of test items within tests must be minimized. For example, significance may be attached, within an individual subject, to the finding of impaired performance in a small number of trials which coincide with epileptiform discharges, relative to performance over the majority of trials where there were no epileptiform discharges (baseline). For TCI findings to be valid in such cases, it needs to be shown that observed differences in cognitive performance with and without EEG discharges are not attributable to the relative difficulty of the test items in each case.

Computer hardware and software

Test programmes were written using QuickBasic 4.5 compiler with PCX Programmers Toolkit - a graphics interface and libraries (Genus Microprogramming Inc, USA, 1991). The test and analysis programmes described in this thesis have been designed by S.G. Coleshill (1999). Test programming was a collaborative venture of S.G. Coleshill and Mr Les Law. The tests were run on a Compaq desktop 486DX/40 MHz computer with a Ranger 5117 VGA high resolution 17 inch colour monitor with flat square tube (Aydin Controls (UK) Ltd). The MicroTouch capacitance touchscreen was attached to the monitor, and the interface was driven by TB driver software (Touch-Base Ltd, UK).

3.3.2. Type of cognitive test

The NGRAMS measures working memory. An event is an occurrence of something at a particular time in a particular place. Therefore, the major constituents of most events are (i) their contents or identity (what?), (ii) their spatial location (where?), and (iii) their occurrence in time (when?). Working memory models invariably assume that working memory consists of dissociable storage and rehearsal processes, with allocation of resources controlled by a 'central executive'. The Baddeley model (1986, 1992a) posits dual working memory mechanisms for rehearsal and maintenance of visuo-spatial material 'the visuo-spatial sketchpad', and for verbal

material 'the articulatory loop', which includes a subvocal rehearsal system, and a phonological store. With Ngrams tasks it is clear that subjects use articulatory rehearsal for unequivocal verbal tasks such as Words, but not for the Corsi. Baddeley (1986) has suggested however, that implicit eye movements to target locations, as in the Corsi, may serve as a rehearsal mechanism for spatial locations. Working memory tasks have been reported in a small number of experiments to be sensitive to hippocampal damage or disruption (Friedman and Goldman-Rakic, 1988).

In verbal working memory, articulatory rehearsal appears to be mediated by frontal regions, with storage mediated by posterior regions (Awh et al., 1996). Significant areas of activation are typically BA7 and BA40 in the parietal cortex, and three regions in the frontal cortex, corresponding to BA44 (Broca's area), and BA6 (premotor and supplementary motor area).

Spatial working memory and spatial selective attention probably share the underlying neural circuitry (Awh et al., 1996). The Corsi Block-Tapping Task (Corsi, 1972), described below in section 5.5.2., is widely considered to be the best available non-invasive test of right hippocampal function (Kolb and Whishaw, 1990), although many investigators have found Corsi's data difficult to replicate (Baddeley and Warrington, 1970; Goldstein and Polkey, 1993). There is good recent evidence that the right prefrontal cortex mediates temporal order information for spatial locations (Kesner et al., 1994), and considerable evidence that the frontal cortex is specialized for temporal order information (Eslinger and Grattan, 1994; Petrides, 1991; Shimamura et al., 1990).

3.3.3. Co-registration of EEG

All cognitive tests were performed during EEG monitoring to co-register EEG events, test stimuli and touch response. The Medelec® Profile EEG system by Taugagreining was used for recording and analysis. Sixteen chlorided silver electrodes were placed according to the Modified Maudsley placement at Fp2, Fp1, F4, F3, F8, F7, C4, C3, P4, P3, T4, T3, T6, T5, O2, O1. The signal was acquired

against the mid parietal electrode Pz reference, filtered (1 to 70 Hz), and analogue to digital converted (sampling frequency 256 hz, 12 bit resolution). ASCII text output from the touch screen and from the test computer was relayed to the EEG recorder in real-time. Memory-resident software enables inputs from the test computer to use the standard facilities of a digital EEG machine to annotate the EEG display. The record is annotated using the manufacture's EEG data acquisition software without modification. This is achieved by means of a memory resident program that generates an interrupt when data appear at the serial port and enters these in the keyboard buffer. The effect is equivalent to the technician keying in even markers and comments during the recording. The markers for stimulus presentation are pre-set, so that when the EEG is analysed for epileptiform discharges (Figure 3.5) the reviewer is able to mark the sheet (Figure 3.6). However, the markers for identity and location of items are masked so the EEG reviewer is blinded to the results of the test.

3.3.4. Ngrams Test

The Ngrams test battery has been developed from the computerized 'Modified Corsi' test, described by Aarts et al (1984). It has been employed until recently for the clinical evaluation of TCI (see section 1.3.) at The Maudsley Hospital, Department of Clinical Neurophysiology. The Modified Corsi test is based in turn on the original Corsi Blocks test (Corsi, 1972). The Modified Corsi test uses 2 working memory tasks, one verbal (sequences of 4-letter words), the other nonverbal (sequences of Corsi Blocks). In both tasks sequences of items are shown on a computer monitor. Reproductions of the verbal or nonverbal sequences were indicated by selection of items with a light-pen (for full details see Aarts et al., 1984).

The name 'Ngrams' is a play on the word 'engram', which refers to the supposed neural representation of learning and memory in the brain. The name also refers to the fact that the number (n) of items or characters (grams) in the presentation of a stimulus string for recall varies.

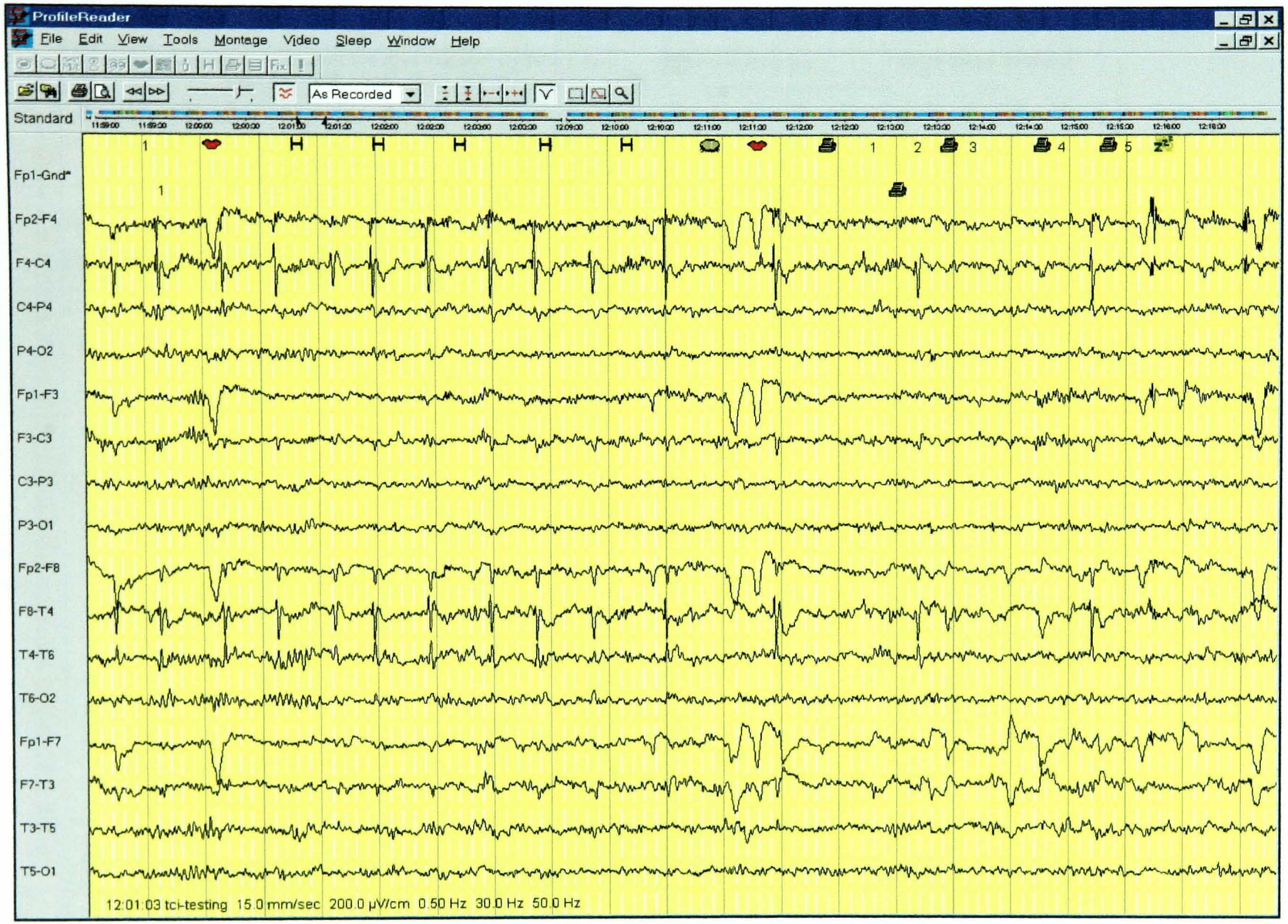


Figure 3.5: EEG screen of a patient with benign epilepsy with centro-temporal spikes during TCI testing (Corsi): trial 11.

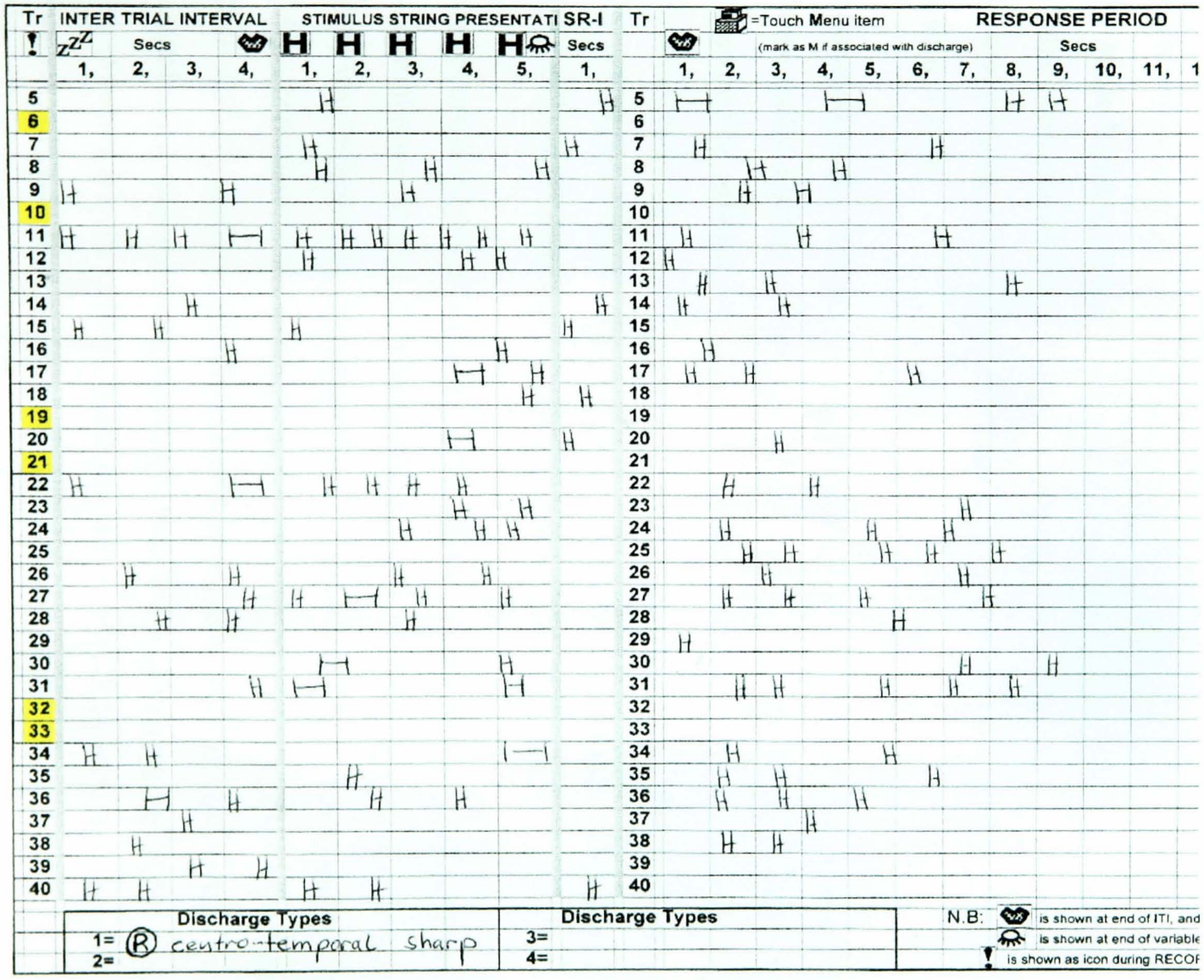


Figure 3.6: Marking sheet for same patient. Note discharges marked at trial 11, corresponding to EEG screen in Fig. 3.7.

Words for Ngrams-words were selected from the 'CELEX Database' of Baayen & Piepenbrock (1993) according to similar word frequency, salience, age-of-acquisition, word imagery and concreteness (Coleshill 1999). Words used in Ngrams were balanced for these attributes. They appear to be the most potent or influential in terms of recognition and recall.

There are several advantages of the Ngrams compared to the Modified Corsi, only some of which are relevant to this study: (1) stimulus material which may potentially be differentially sensitive to cognitive changes in different brain regions, e.g., amygdala, hippocampus, lateral temporal and frontal cortex, etc.; (2) option to test stimulation-induced epileptiform discharges; (3) the verbal and nonverbal stimulus items in the Ngrams are optimised in terms of the balancing of stimulus attributes and have been empirically quantified (Coleshill, 1999); (4) including reaction time and serial position analysis as measurements (for full details see PhD data, S.G. Coleshill, 1999).

The duration of the TCI test is of crucial importance as cognitive testing can suppress ID, but usually discharges will return after a while. Furthermore a certain number of trials have to be measured in order to be able to perform statistical analysis. Similarly to the traditional Corsi test (Aarts et al. 1984), each subtest consists of 40 trials, 4 of which are practice trials. The test was self-paced and depending on the memory capacity and speed of each child lasted between 30 and 45 min.

The test consists of presenting a sequential string of items on the touch-screen within a 3x4 spatial array. Recall of the string (item, order of item, location and order of location) was indicated by the subject by touch-selecting items from a menu of 12 possibles, then entering them into the array. Items appeared in a pseudo-randomised sequence. Pseudo-randomisation was used to minimise heterogeneities and unpredictable interactions between stimuli, which would make some trials more difficult to remember than others. It can be used as a working memory test or in combination with real-time EEG co- registration as a TCI test.

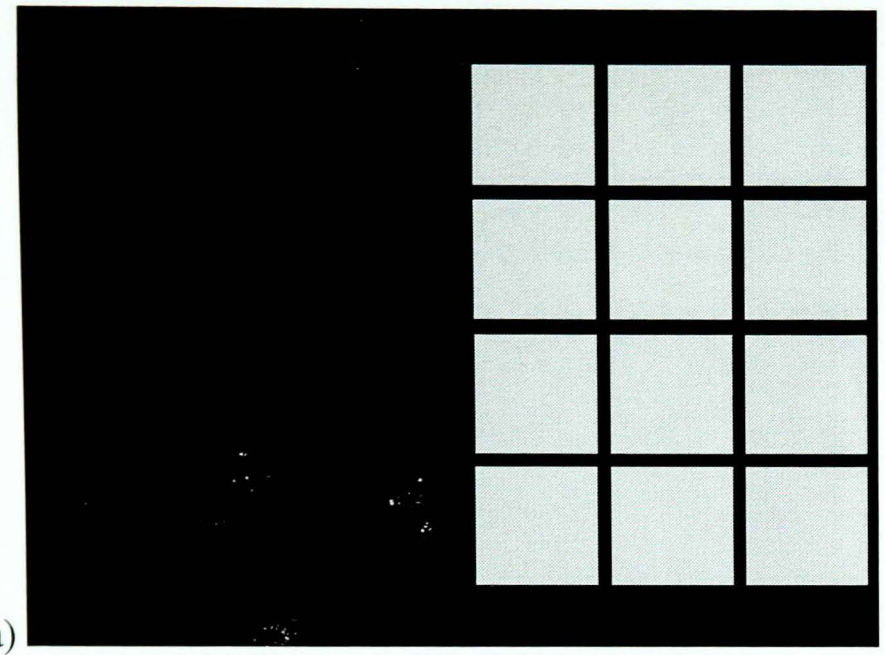
The test may be considered as a series of trials, each comprising, first, the presentation of the stimulus sequence (duration 3-5 sec), then a one-sec stimulus-

response interval, followed by the response phase with variable duration. Before the next trial there is an intertrial interval of 4 sec.

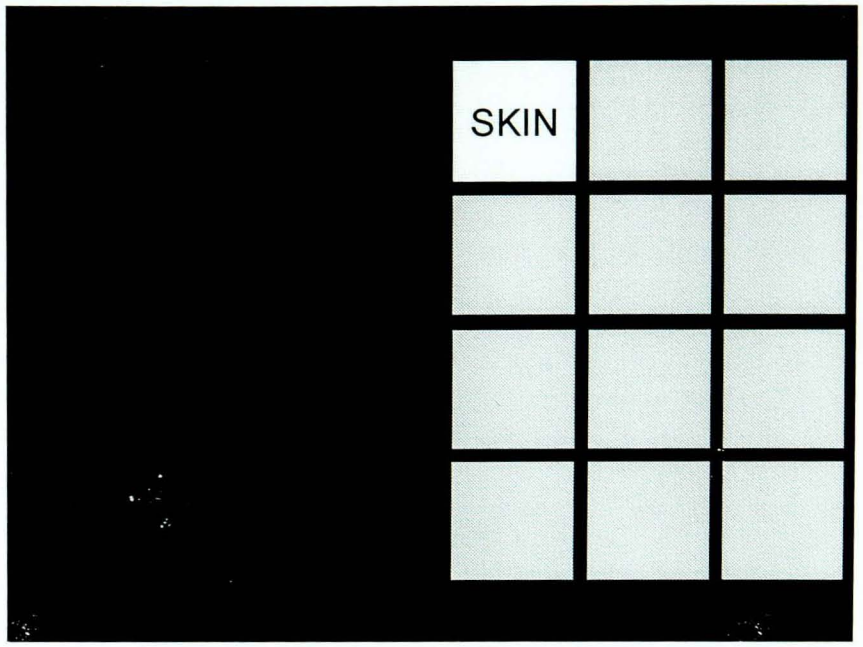
Figure 3.7 illustrates a trial of Words: a) the patient is presented with an empty spatial array for 1 sec. b) Stimulus presentation begins with the first item 'SKIN' being shown within the spatial array for 1 sec. c) After the first item extinguishes the second item 'HAIR' appears, d) than the third 'WALL'. The screen then cleares during a 2 sec stimulus-response interval e) before showing two 3x4 spatial arrays, on the left the menu array, on the right the clears original array. f) Stimulus response. The task requires reproduction of the string 'SKIN-HAIR-WALL' from stimulus presentation in sequence order. The first item 'SKIN' is touch selected from the menu on the left of the screen, then touched into the location within the spatial array. g) The second item 'HAIR' in the string recalled from stimulus presentation is selected from the menu then touched into the location within the spatial array. h) The final third item 'WALL' in the string recalled from stimulus presentation is selected. Trial ends. The screen is cleared for a 4 sec intertrial interval before the next trial begins.

Figure 3.8 illustrates a trial of Ngrams-corsi: a) the patient is presented with an empty spatial array for 1 sec. b) Stimulus presentation begins with the first items being shown within the spatial array for 1 sec. c) After the first item is extinguished the second item appears, d) then the third. The screen then clears during 2 sec stimulus-response interval e) before showing two 3x4 spatial arrays on the left the menu array, on the right the cleared original array. f) Stimulus response. The task requires recall of the string from stimulus presentation in sequence order. The first item is touch selected from the menu on the left of the screen, then touched into the location within the spatial array. g) The second item in the string recalled from stimulus presentation is selected from the menu then touched into the location within the spatial array. h) The final third item in the string recalled from stimulus presentation is selected and touched into the spatial array. The screen then clears for a 4 sec intertrial interval before the next trial begins.

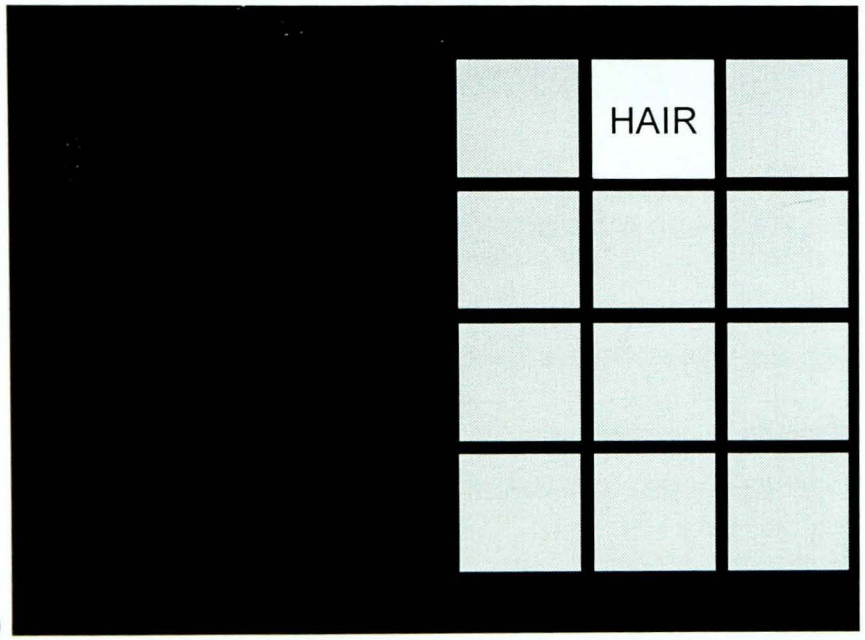
a)



b)



c)



d)

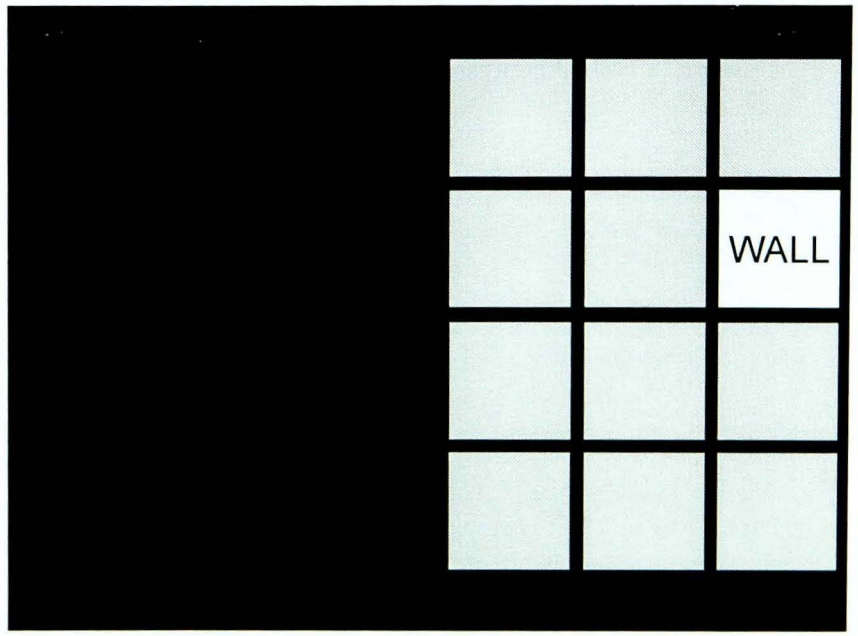


Figure 3.7 a-d: N-Grams Words (description see text)

e)

SEAT	SKIN	LAND			
ROAD	FISH	WIFE			
HAIR	LINE	FIRE			
ROCK	WALL	HILL			

f)

SEAT		LAND	SKIN		
ROAD	FISH	WIFE			
HAIR	LINE	FIRE			
ROCK	WALL	HILL			

g)

SEAT		LAND	SKIN	HAIR	
ROAD	FISH	WIFE			
	LINE	FIRE			
ROCK	WALL	HILL			

h)

SEAT		LAND	SKIN	LINE	
ROAD	FISH	WIFE			WALL
HAIR		FIRE			
ROCK		HILL			

Figure 3.7 e-h: N-Grams Words (description see text)

PAGE NUMBERING AS IN THE ORIGINAL THESIS

Chapter 4: Factors influencing the incidence of interictal discharges

4.1. Summary

Objective: This chapter aims to document the frequency of interictal EEG discharges in children with well-controlled epilepsy and assesses the effects of a number of intrinsic and extrinsic factors on the incidence of interictal discharges.

Method: Children with well-controlled epilepsy underwent ambulatory EEG recording which was analysed visually. Neurological examination, detailed history, parents and teachers' behavioural scales (Conners' rating scales) and IQ tests were performed and compared to the results of the EEG.

Results: Thirty-three out of fifty children had interictal discharges. The incidence was significantly higher in boys ($p<0.01$) and in children with idiopathic partial epilepsy ($p<0.05$) and lower in children taking sodium valproate ($p<0.05$). Age of onset of epilepsy, age, presence of neurological abnormalities, IQ and behaviour did not influence the incidence of discharges. In addition, there was a significant interaction between the factors gender and type of epilepsy.

Conclusion: Our data suggest that interictal discharges are very common even in children with well-controlled epilepsy. Gender and type of epilepsy may influence the incidence of interictal discharges.

4.2. Introduction

Interictal discharges or subclinical epileptiform discharges in repeated EEG recordings occur in up to 90% of patients with ongoing epilepsy (Ajmone Marsan and Zivin, 1970). As some discharges are accompanied by transient changes in motor (Tassinari et al., 1998) or cognitive function (Aarts et al., 1984, Binnie and Marston, 1992), the distinction between clinical and subclinical events may depend on the assessment method used. Factors affecting interictal discharges in adults with epilepsy include the proximity of EEG recording to seizures (Ajmone Marsan and Zivin, 1970, Sundaram et al., 1990) and seizure frequency in the preceding year (Sundaram et al., 1990). Neither age at the time of the recording, neurological status and aetiology of epilepsy influenced the frequency of interictal discharges (Sundaram et al., 1990), nor did drug levels (Gotman and Marciani, 1985). Adults are less likely to have interictal discharges than children, particularly if the epilepsy first presented in adulthood (Ajmone Marsan and Zivin, 1970, Salinsky et al., 1987). Some childhood epilepsy syndromes are known to be associated with frequent interictal discharges, for example benign epilepsy with centro-temporal spikes, the commonest idiopathic epilepsy syndrome of childhood. The effect of anticonvulsants is still unclear. A survey of clinical trials in epilepsy (Gram et al., 1982) has shown that two-thirds of rigorously designed controlled trials include EEG recordings but only half of these present a statistical analysis of the findings.

The fluctuating nature of both spontaneous seizures and interictal discharges make it difficult if not impossible to draw meaningful conclusions from random routine EEG recordings (Milligan and Richens, 1981). Subclinical EEG discharges occur at anytime within a 24-hour period but random 20 minutes EEG recordings sample only a small fraction of the activity occurring during a 24 hour period (Stevens et al., 1972). It is known that this pattern is frequently modulated by extrinsic or intrinsic factors, which influence the overall discharge probability (Kellaway et al., 1980, Binnie et al., 1984). Assessments of the therapeutic response based on random EEGs are therefore likely to be inaccurate (Binnie, 1982). The fluctuating nature of interictal discharges explain why they are not observed in each random EEG recording in individual patients (Ajmone Marsan and Zivin, 1970, Salinsky et al.,

1987). The circadian pattern and day-to day variability of interictal discharges are relevant to the use of long-term EEG recording as a means of assessing therapy.

The incidence of EEG discharges in children with well-controlled epilepsy has not been adequately documented. This is of importance for two reasons: 1) EEG are frequently requested in such children to monitor success of treatment and to estimate the risk of seizure recurrence if AED are withdrawn (Duncan, 1987) and 2) interictal discharges can cause transitory cognitive impairment (TCI) and therefore may have consequences for the psychosocial function of children with epilepsy (Aarts et al., 1984, Binnie and Marston, 1992; Marston et al., 1993).

The aims of this chapter were to evaluate interictal discharges in children with well-controlled epilepsy and correlate incidence and frequency of discharges to gender, age, family history, type of epilepsy, age of onset, IQ, current seizures and current antiepileptic drugs.

4.3. Methods

4.3.1. Patients

For this chapter a subgroup of well-controlled patients were included in the analysis. Well-controlled epilepsy was defined as being seizure-free over the last three months or having had only one seizure per month in this period, but where seizure control was considered optimal and no further modification to the anti-epileptic drug regimen was planned. For patient recruitment see chapter 3.5

4.3.2. Procedure

Physical and neurological examination, routine and ambulatory EEG as well as IQ-tests (WISC-R III, Wechsler Intelligence Scale for children-Revised version) were performed. In addition a detailed history was obtained including family history, seizure history, social history and medication. The Conners' rating scales for parents and teachers were used to evaluate behaviour. A score over 70 (+2 SD) in at least one

subscore was considered as abnormal. Seizures and epileptic syndromes were classified according to the International League against Epilepsy classification of epilepsy syndromes (1981, 1989).

Discharges were quantified in each patient during the eyes-open phase of a 12 to 24 hour period as discharge frequency (number per hour) and discharge time per hour (duration in seconds per hour). For details of ambulatory EEG monitoring and quantification of EEG discharges see section 3.4.

4.3.3. Statistical analysis

The following factors were correlated with the presence of ID in the ambulatory recording using the chi-square test (2-tailed):

1. Age of the patient at the time of the recording: (a) 7-9 years, (b) 10-13 years and (c) 14-17 years.
2. Gender.
3. Age of onset: (a) ≤ 4 years, (b) 5 - 7 years and (c) ≥ 8 years.
4. Type of epilepsy: (a) idiopathic partial, (b) idiopathic generalised, (c) symptomatic partial and (d) symptomatic generalised.
5. Intelligent quotient: (a) ≤ 84, (b) 85 – 115 and (c) > 115.
6. Behaviour: (a) normal, (b) abnormal.
7. Neurological examination: (a) normal, (b) abnormal.
8. Antiepileptic drugs: (a) none, (b) carbamazepine, (c) valproate, (d) other antiepileptic drugs, including combinations.
9. Seizures in the 4 weeks preceding the recording: (a) no, (b) yes.
10. Frequency of seizures in the last year: (a) none, (b) 1 – 10 and (c) > 10.

The interaction between was analysed using binary logistic regression for qualitative variables and ordinal logistic regression for quantitative variables (SPSS 10). Statistical significance was accepted at the level of $p<0.05$.

4.4. Results

4.4.1. Clinical findings

Fifty patients were included in the study (30 males, 20 females; median age: 11 years with a range of 7 – 17 years). Fourteen children had idiopathic partial epilepsy (9 benign epilepsy of childhood with centro-temporal spikes, 3 benign epilepsy with occipital paroxysms, 2 atypical benign partial epilepsy), 11 children had idiopathic generalised epilepsy (6 childhood absence epilepsy, 1 juvenile absence epilepsy, 4 juvenile myoclonic epilepsy) and 25 symptomatic partial epilepsy. Six patients were not receiving antiepileptic drugs, 23 were on carbamazepine monotherapy, 13 on sodium valproate monotherapy, 1 on phenytoin monotherapy, 1 on vigabatrin monotherapy and 6 on a combination (carbamazepine and vigabatrin, carbamazepine and valproate, carbamazepine and acetazolamide, clobazam and ethosuximide, valproate and phenytoin). Most children (78%) were seizure free during the three months preceding recrutment. Of the 11 children with seizures eight (16%) had one seizure in the last four weeks and only two patients had seizures in the last week. Table 1 summarises the patients' demographics.

Number of patients	50
Age – median (years)	11 (range 7-17)
Gender – male	30 (60%)
Positive family history	11 (22%)
IQ – median	94 (range 60-135)
Age of onset (years)	6 (range 0-15)
Seizures in last	
4 weeks	8 (16%)
1 week	2 (4%)

Table 4.1: Characteristics of patients

4.4.2. EEG findings

The mean duration of the ambulatory EEG recording was 18.12 hours (SD ±4.46). Thirty-four (66%) children had subclinical discharges in the awake state. Discharges were generalised in 7 patients, focal in 15 (right sided in 6, left sided in 3 and bilateral in 6) and both focal and generalised in 12 patients (with focal discharges right sided in 7, left sided in 2 and bilateral in 3). In children with interictal discharges the median frequency of discharges was 4.25/hr (range 0.6 to 115.6/hr, SD 26.83) and the median duration of discharges was 5.45 sec/hr (range 1.0 to 140.8 sec/hr, SD 34.20).

There was a high correlation between frequency of discharges and duration of discharges (Pearson's Correlation Coefficient $r=0.962$; $n=51$; $p<0.001$). The relationship of interictal discharges to various factors described previously is summarised in Table 2. Age, age of onset, IQ and presence of behaviour problems or neurological abnormalities did not influence interictal discharges. However, there was a tendency for children with idiopathic epilepsy and interictal discharges to have more behavioural problems (11 out of 19) than children with idiopathic epilepsy but without interictal discharges (1 out of 6). This difference did not quite reach the statistical significance ($\chi^2=3.105$; $df=1$; $p<0.1$). Boys showed significantly more interictal discharges than girls ($\chi^2=6.551$; $df=1$; $p<0.01$). The incidence of discharges was higher in patients with idiopathic partial epilepsies ($\chi^2=6.257$; $df=2$; $p<0.05$) than patients with idiopathic generalised epilepsies or symptomatic partial epilepsies. Patients taking sodium valproate had significantly fewer discharges than patients not taking AED or taking other AEDs ($\chi^2=9.823$; $df=3$; $p<0.05$).

There was a tendency for patients with a close proximity to seizures to have ID. Of the 8 children with seizure in the last four weeks prior to study entry, 7 (88%) had ID, whereas 26 out of 42 (62%) children without seizures in this period had discharges. This difference was not significant perhaps because the number of patients with seizures was small ($\chi^2=1.962$; $df=1$; ns). The incidence of idiopathic partial epilepsies was not significantly higher among boys (9 out of 30 boys - 30%) than among girls (5 out of 20 - 25%).

	No. of patients in this category	No. of patients with ID (Chi-square)	ID frequency mean [1/hr] (ANOVA)
Total	50	33 (67%)	11.3
Age (years)			
(a) 7-9	14	10 (71%)	29.2
(b) 10-13	19	12 (63%)	5.8
(c) 14-17	17	11 (65%)	4.5
Gender			
(a) male	30	**24 (80%)	17.0*
(b) female	20	9 (45%)	1.6
Age of onset (years)			
(a) 0 – 4	17	11 (65%)	12.8
(b) 5 - 7	17	11 (65%)	16.9
(c) ≥ 8	16	11(69%)	5.0
Type of epilepsy			
(a) idiopathic partial	14	*13 (93%)	28.4
(b) idiopathic generalised	11	6 (55%)	3.4
(c) symptomatic partial	25	14 (56%)	5.5
IQ			
(a) < 85	17	12 (71%)	5.0
(b) 85 – 115	25	16 (64%)	18.7
(d) > 115	8	5 (63%)	4.0
Behaviour			
(a) normal	27	18 (67%)	10.2
(b) abnormal	23	15 (65%)	13.5
Neurological examination			
(a) normal	44	28 (64%)	12.5
(b) abnormal	6	5 (83%)	6.3
Antiepileptic drugs			
(a) none	6	5 (83%)	21.1
(b) carbamazepine	23	18 (78%)	18.5
(c) sodium valproate	13	* 4 (31%)	0.4
(d) other, incl. combinations	8	6 (75%)	3.5
Seizures in last 4 weeks			
(a) no	42	26 (62%)	10.2
(b) yes	8	7 (88%)	20.4
Seizures in last year			
(a) no seizures	15	10 (67%)	9.6
(b) 1-10 seizures	28	20 (71%)	11.7
(b) ≥ 11 seizures	6	3 (50%)	17.4

*p<0.05, **p<0.01

Table 4.2: Relationship of interictal discharges (ID) to age, gender, family history, neurological examination, IQ, behaviour, age of onset, type of epilepsy, antiepileptic drugs and seizures frequency.

Naturally, children with idiopathic generalised epilepsy were significantly more likely to receive sodium valproate (8 out of 11) and children with partial epilepsy were significant more likely to receive carbamazepine (9 out of 14 with idiopathic partial epilepsy and 13 out of 25 with symptomatic partial epilepsy) (χ^2=27.973; df=6; p<0.001).

As the distribution of discharge frequency was not normal, data were divided into three approximately equal groups (no ID, 1-19 ID per hour, more than 20 ID per hour). There was a significant main effect for the factors 'gender' (F(1,33) = 9.30; p<0.01) and 'type of epilepsy' (F(1,33) = 9.80; p<0.01) on the number of discharges but not for the factor 'antiepileptic drugs'. In addition, to the main effect there was a significant interaction between gender and epilepsy (F(2,33) = 3.35; p<0.05). Boys with idiopathic partial epilepsy had more discharges than girls with idiopathic partial epilepsy; this gender difference was not evident for idiopathic generalised or symptomatic partial epilepsy (Figure 1).

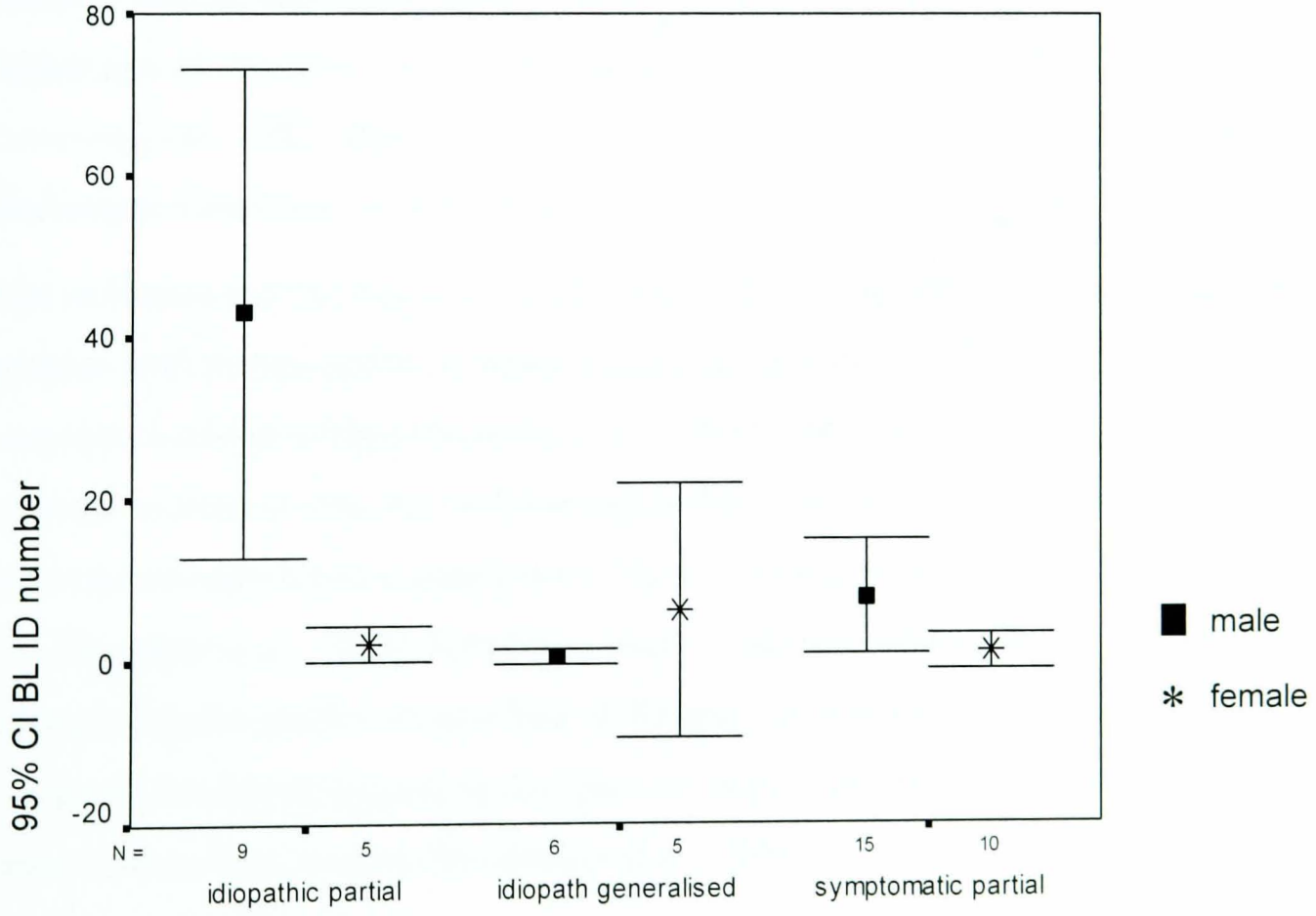


Figure 4.3: Distribution of frequency of discharges (per hour) in respect to gender and type of epilepsy. CI: confidence interval.

4.5. Discussion

The results of this study show that two thirds of children with well-controlled epilepsy have interictal discharges which occur significantly more often in boys than girls and in benign partial epilepsy. Our group of patients with well-controlled epilepsy appear representative of the population of school-age children with epilepsy: nearly 50% symptomatic epilepsies, 25% idiopathic partial epilepsies and 25% idiopathic generalised epilepsies (Cavazzuti, 1980); the latter including approximately 13% childhood absence epilepsy, 10% juvenile myoclonic epilepsy and 2% juvenile absence epilepsy. As expected there were more boys than girls and the IQs were within the normal range but somewhat below average (Ellenberg et al., 1986; Rodin, 1989).

There is evidence that the risk of seizure recurrence after AED withdrawal is increased if discharges are present beforehand. In adults the finding of discharges in an EEG is of uncertain prognostic significance (Overweg et al., 1987). In contrast, in children with epilepsy, EEG abnormalities (slowing or epileptiform) correlate with a higher rate of seizure recurrence after drug withdrawal (Caviedes and Herranz, 1998, Emerson et al., 1981, Shinnar et al., 1985). Thus, it was surprising that epileptiform discharges were found in 69% of children with well-controlled epilepsy.

The incidence and the frequency of ID were both significantly higher in boys and in patients with benign partial epilepsy. Gender differences in epilepsy have been reported in animal studies (Standley et al., 1995, Todorova et al., 1999). In NMDA-induced seizures in rats, the initial severe seizure was similar in males and females, but male rats developed a significantly higher ongoing seizure activity than female rats (Standley et al., 1995). Recently a study in patients with refractory temporal lobe epilepsy found a greater volume loss of the brain in quantitative MRI in men compared to women suggesting that men are more vulnerable to seizure-associated brain damage than woman (Briellmann et al., 2000).

It is well known that children with benign epilepsy with centro-temporal spikes have frequent interictal discharges occurring in up to 70% of these children during wakefulness and in almost all during drowsiness and sleep (Degen et al., 1988, Holmes, 1992). Furthermore, there was a significant interaction between gender and

type of epilepsy: boys with benign partial epilepsy were most likely to have discharges compared to girls or boys with other types of epilepsy.

It is generally believed that disappearance of interictal discharges from the EEG parallels an improvement in seizure control although the evidence for this is controversial. Binnie reported only a very weak association between changes in seizure frequency and in the amount of interictal discharges seen in 1244 routine EEGs (Binnie, 1982). However, in a study of 26 patients with partial epilepsy who had 13-hour EEGs, there was a positive correlation between seizure frequency and the amount of interictal discharges (Autret et al., 1983). Similarly, Sundaram and colleagues (1990) found discharges significantly more often in patients with seizures in the two days before the recording and with more than 12 seizures per year. We found a tendency for children with seizures within the last four weeks to be more likely to have interictal discharges, but none of our patients had seizures within 2 days of the EEG recording. We could not confirm a correlation between the number of seizures per year and incidence of interictal discharges.

There is evidence that interictal discharges are associated with cognitive and behavioural problems in children with epilepsy. Stores and colleagues (Stores, 1973) demonstrated significantly more behavioural disturbances in boys with left temporal discharges than in boys with epilepsy but without inter-ictal discharges. Dodrill and Wilkus (Dodrill and Wilkus, 1976) found in adults with epilepsy a significant association between lower intelligence scores and the presence of discharges, especially generalised discharges occurring more than once per minute. In our group of patients there was no difference between children with and without interictal discharges in respect to their behaviour. Children with symptomatic epilepsy are more much likely to have behavioural problems then children with idiopathic epilepsy, probably as a result of the combination of a brain lesion and seizure related factors rather than epilepsy related factors alone (Rutter et al. 1970).

Similarly children with and without interictal discharges did not differ in their IQ. However the IQ is only a very rough measurement of cognitive function. In addition, only patients with an IQ > 60 were analysed. Thus, we found no evidence that interictal discharges is a marker or cause of behavioural or cognitive problems in

children with well-controlled epilepsy attending mainstream school. This needs to be evaluated in further studies involving TCI testing. The only way to establish whether discharges are causing cognitive and behavioural problems in children with epilepsy or are co-existing phenomena of an underlying defect, is by finding an improvement of cognition and behaviour when EEG discharges are suppressed.

For seizures other then absences, there is generally not a clear relationship between control of seizures and interictal discharges (Duncan, 1987; Milligan and Richens, 1981). In fact some drugs, for example carbamazepine, are known to cause deterioration in the EEG while at the same time improving seizure control (Wilkus et al., 1978). There is some evidence that barbiturates (Kellaway et al., 1978), sodium valproate (Adams et al., 1978) and lamotrigine (Binnie et al., 1986; Marciani et al., 1996) may suppress interictal discharges more than other AEDs. In concordance with this we found significantly fewer interictal discharges in patients on sodium valproate compared to other AEDs or patients not on AEDs. This is at least partially due to the fact that children with absence epilepsy are likely to be on sodium valproate. It is well recognised that in contrast to other epilepsy types there is a clear association between control of seizures and interictal discharges in typical childhood epilepsy (Duncan, 1987). It was not surprising therefore that in the factorial analysis no significant difference between AEDs was found.

The interaction between interictal discharges and AED in childhood absence epilepsy also explains why in our study children with idiopathic partial epilepsy were more likely to have interictal discharges than children with idiopathic generalised epilepsy – since more than half of the latter are children with absence epilepsy. It is well recognised that patients with symptomatic epilepsy, particularly temporal lobe epilepsy, frequently lack interictal discharges in the surface recording. As idiopathic partial epilepsy syndromes are age related this may explain that other studies looking at interictal discharges in adults have not found a difference related to type of epilepsy (Sundaram et al., 1990).

This finding has implications for the management of children with epilepsy as it makes evident that in individual patients, an EEG is not helpful for the decision whether or not to stop AEDs.

Chapter 5: Effect of lamotrigine on interictal discharges

5.1. Summary

Objective: To document the spontaneous fluctuations of interictal discharges, and to evaluate the effect of lamotrigine on interictal discharges in children with well-controlled epilepsy.

Method: Sixty-one patients aged 7-17 years were included in a double blind, placebo-controlled, cross-over study. Lamotrigine or placebo was added to the current antiepileptic drug regime in each treatment period of 12 weeks. Ambulatory EEG recordings were carried out during baseline, placebo and drug phases. The amount of interictal discharges was compared between baseline and placebo to estimate spontaneous fluctuations and between placebo and lamotrigine to estimate the effect of the drug.

Results: 70% of patients had interictal discharges at baseline. Thirteen patients withdrew before trial completion. The spontaneous fluctuations of discharges in ambulatory recordings were considerable; frequency and duration varied more within than between subjects. Lamotrigine reduced the duration of discharges per hour ($p<0.05$), but not the total number per hour. Twenty-two out of 35 patients with interictal discharges showed a reduction of duration of discharges in the lamotrigine phase.

Conclusion: Inter- and intra-individual variations of interictal discharges make it difficult to evaluate the effect of antiepileptic drugs on discharges even if prolonged EEG recordings are used. Lamotrigine appears to have an effect on the termination rather than the initiation of discharges.

5.2. *Introduction*

Interictal or 'subclinical' epileptiform discharges occur in up to 90% of patients with ongoing epilepsy although they not necessarily in every EEG recording (Ajmone Marsan and Zivin, 1970). Aarts et al. (1984) defined discharges as subclinical where 'the available methods of clinical observation ... fail to show any changes in the patient'. Such discharges are often not truly subclinical as they have been shown to cause brief disruptions of cognitive performance (see chapter 8). This leads to the question as to whether treatment of discharges with AED improves psychosocial function (see chapter 6 and 7). In order to do this the effect of AED on interictal discharges must first be established having in mind the nature of spontaneous fluctuation of such discharges. A survey of clinical trials in epilepsy (Gram et al., 1982) showed that two-thirds of rigorously designed controlled trials included EEG recordings but only half of these presented an analysis of the findings, which were mostly negative.

The effect of anticonvulsant is still unclear (see section 1.3.7.2), but most AEDs which suppress discharges have a negative effect on cognition or behaviour.

Lamotrigine is a wide-spectrum antiepileptic drug that is effective in all forms of epilepsy. The pharmacokinetic profile may be considered ideal when the drug is used as monotherapy; kinetic interactions complicate dosing schedules when it is used for add-on treatment. It is better tolerated than most long-established antiepileptic drugs, and in particular is said to have few or no effects on cognition and behaviour. Lamotrigine has also been shown to suppress interictal discharges in patients with epilepsy (Binnie et al., 1986; Erikson et al., 2001). For more details on lamotrigine see section 1.5.

The variability of both spontaneous seizures and interictal discharges make it difficult to draw conclusions from random routine EEG recordings (Milligan and Richens, 1981). The temporal variability of EEG phenomena in children with epilepsy has not been adequately documented. Drug effects therefore may be undetectable unless the discharges show little intra-individual variability. Few studies address day-by-day variability of interictal discharges in patients with secondary epilepsy (Martins da Silva et al., 1984) or primary generalised epilepsies (Burr and Stefan, 1987) and only one included a few children (Mayr et al., 1989).

The objective of this part of the study was to determine the range of spontaneous fluctuations of interictal discharges and whether lamotrigine had an effect on discharge frequency in children with no or few seizures using 24-hour ambulatory recordings.

5.3. Methods

5.3.1. Patients

Patients were recruited from pediatric outpatient clinics at three study sites: Guy's Hospital, King's College Hospital and The National Centre for Young People with Epilepsy (NCYPE, former St Piers Lingfield), UK. Patients aged 7 to 17 years were eligible if they had a confident diagnosis of epilepsy and were seizure free or were having occasional seizures but in whom the responsible clinician or parent/careers felt that further adjustments to AEDs was not warranted. For more details on patient recruitment and inclusion criteria see section 3.5.

5.3.2. Procedure

This was a double blind, randomised, placebo-controlled, cross-over study with lamotrigine. See section 3.6 for study protocol (Figure 3.7 and Table 3.2) and dosage regime (Table 3.1).

5.3.3. Efficacy and Safety Assessments

See section 3.4 for assessment of interictal discharges and section 3.6 for safety assessment.

5.3.4. Statistical analysis

The outcome variables were the percentage change in the number of EEG discharges per hour and in the duration of discharges in seconds per hour. To determine the spontaneous fluctuations of interictal discharges, discharge frequency and duration at

baseline and on placebo were compared using the Wilcoxon signed ranks test. It was expected that the data would be skewed, as a large proportion of children with well-controlled epilepsy will have few discharges or none at all. Therefore, values were transformed as suggested by Burr and Stefan (Burr and Stefan, 1987). Instead of using the transformation $d^{\wedge} = d^{0.2}$, first values of 0.00 were recorded as 0.001 in order to perform analysis on all data and then values were log transformed. The same transformation and tests were used to examine the effect of lamotrigine by comparing discharge frequency and duration on placebo and lamotrigine.

ANCOVA (general linear model, SPSS 10.0 for Windows) was used to test for a possible order effect and chi-square test to determine whether epilepsy-related factors influenced the effect of lamotrigine. In an "as-treated" analysis of changes in the frequency of discharges, data of patients who stopped the treatment early included data obtained only before treatment was discontinued. Analysis was by intention to treat. All tests were 2-tailed.

Safety evaluation used descriptive analysis of the frequency with which patients reported specific adverse events.

5.4. Results

5.4.1. Clinical findings

Of the 64 children screened, 61 patients were included (39 males, 22 females; mean age: 11.5 years, range 7-17 years). All patients underwent randomisation and entered the single-blind baseline phase; 31 were randomised to receive first lamotrigine and then placebo and 30 the reverse order. However, two children were not enrolled in the treatment phase: one had deterioration in seizure control and the parents of one withdrew consent. Figure 5.1 illustrates the trial profile.

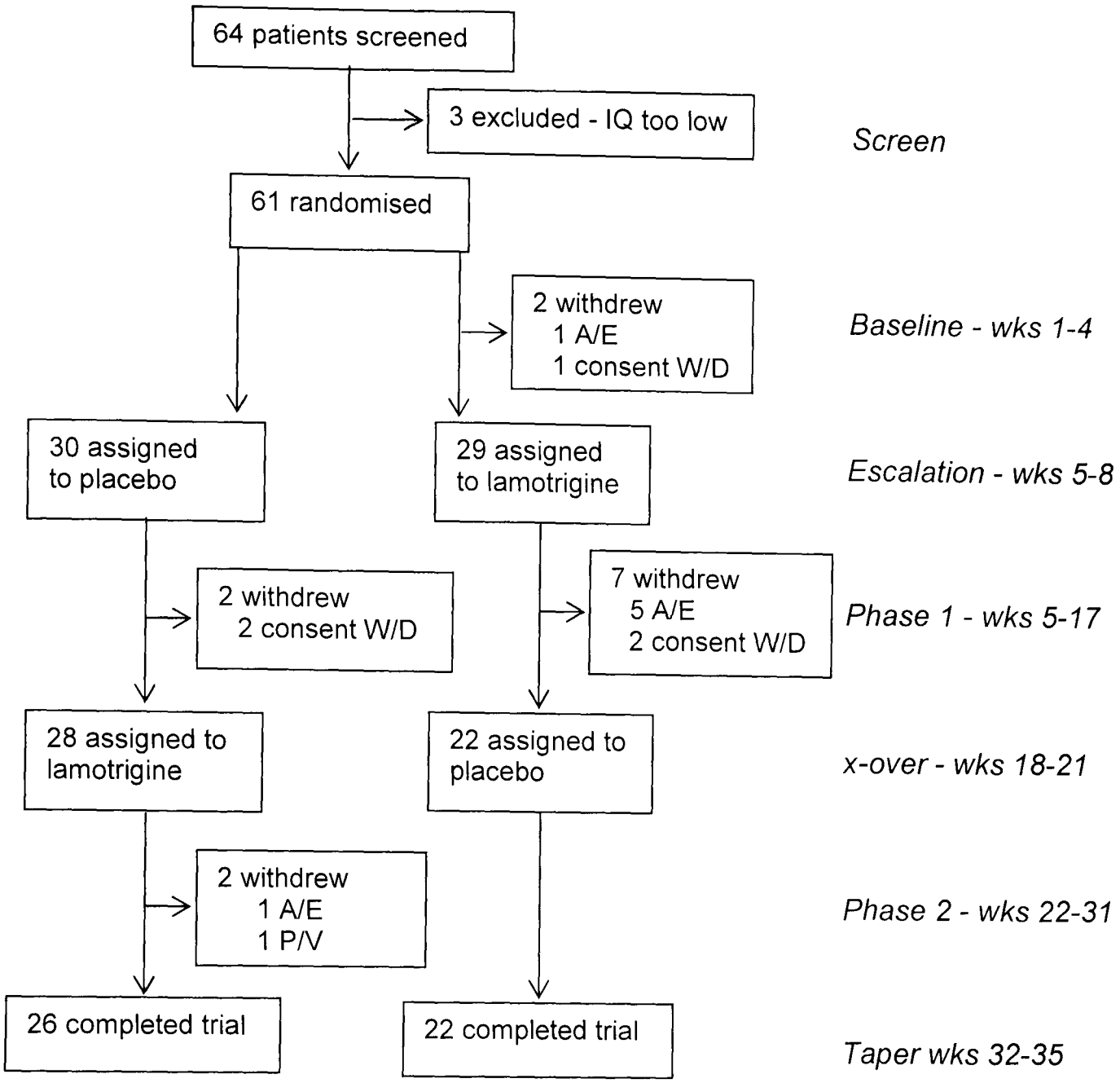


Figure 5.1: Trial profile

Legend: A/E: adverse events, W/D withdrawn, P/V protocol violation, wks: weeks.

The characteristics of both groups were similar (Table 5.1); a few more children in the group lamotrigine/placebo had seizures in the three months preceding baseline and were somewhat younger when their epilepsy began, but these differences were not significant. Sixteen children had idiopathic partial epilepsy (ten benign epilepsy of childhood with centro-temporal spikes, three benign epilepsy with occipital paroxysms, three atypical benign partial epilepsy), 19 children had idiopathic generalised epilepsy (one infantile myoclonic epilepsy, nine childhood absence epilepsy, three juvenile absence epilepsy, six juvenile myoclonic epilepsy) and 26 symptomatic partial epilepsy.

Seven patients were not receiving antiepileptic drugs, 23 were on carbamazepine monotherapy, 21 on sodium valproate monotherapy, one on ethosuximide monotherapy, one on phenytoin monotherapy, one on vigabatrin monotherapy and seven on a combination (carbamazepine and vigabatrin, carbamazepine and valproate, carbamazepine and acetazolamide, clobazam and ethosuximide, sodium valproate and phenytoin).

Most children (77%) were seizure free during the three months preceding baseline. Eight children had up to two partial seizures per month, two between three and five absences per month and four had more than six absences per month, but no more than three absences on any one day (Table 5.1). One patient had five partial seizures three months prior to baseline during a febrile illness, but only two per month in the two months prior to entry.

Thirteen children were withdrawn from the study (including the two children who did not enter the treatment phase): seven had adverse events (including one in the single blind placebo phase), parents of five children withdrew consent (including one in the single blind placebo phase) and one had protocol violations. Eight of these children had discharges. Four children were in the placebo/lamotrigine randomisation group and nine in the lamotrigine/placebo randomisation group; this difference was not significant (χ^2=2.24; df=1; ns).

A plasma lamotrigine level was available in 24 children, in 24 the sample was either lost or the blood test failed and 13 were withdrawn from the study before the maintenance dose was reached. The mean plasma lamotrigine concentration among patients who received the prescribed total daily maintenance dose for their weight was 5.9 μg/ml (SD ±3.5). Ten children had a level of ≤ 5 μg/ml and 14 children a level >5 μg/ml. There was no correlation between the plasma concentration of lamotrigine and discharge frequency or duration.

Characteristic	LTG/Placebo	Placebo/LTG
Number of patients	31	30
Age in years - mean (range)	11.4 (7-17)	11.7 (7-17)
Sex – male number	20 (65%)	19 (63%)
Race		
White	23	25
Black	5	2
Other	3	3
IQ (WISC) – mean (SD)	93.1 (17.2)	98.6 (22.1)
Verbal IQ	96.6 (16.0)	105.3 (20.1)
Non-verbal IQ	90.5 (17.4)	90.3 (23.1)
Age of onset in years - mean (range)	5.5 (0-15)	7.8 (3-15)
Type of epilepsy		
IGE	8	11
IPE	10	6
SPE	13	13
Concomitant antiepileptic drugs		
None	3	4
Carbamazepine	12	11
Sodium valproate	10	11
Other*	3	0
Any combination	3	4
Seizures/month†		
No seizures	22 (71%)	25 (83%)
1-2 seizures	5 (16%)	1 (3%)
3-5 seizures	3 (10%)	1 (3%)
≥ 6 seizures	1 (3%)	3 (10%)
ID in initial ambulatory EEG	21 (68%)	21 (70%)

Table 5.1: Baseline characteristics of patients

Legend: LTG, lamotrigine; ID, interictal discharges. *Other antiepileptic drugs included ethosuximide, phenytoin and vigabatrin; † in 3 months prior study.)

The seizure frequency did not change significantly during the study (Table 5.2). Forty-seven patients were seizure free at baseline (77%), 40 during the placebo phase (78%) and 39 during the lamotrigine phase (81%). In the three months preceding baseline the mean seizure frequency was 3.43 (SD 13.4, range 0-90) seizures per month, during the placebo phase 3.24 (SD 10.38, range 0-50) seizures per month and during the lamotrigine phase 3.21 (SD 14.69, range 0-90). The wide range was caused by patients with absence seizures. If these were excluded the ranges changed to 0-5 seizures per month at baseline, 0-8 during placebo and 0-3 during lamotrigine. Seven patients had a reduction of seizures of more than 50% during the lamotrigine phase compared to placebo and five patients had a reduction of seizures of more than 50% during the placebo phase compared to lamotrigine.

Seizure type	improved	seizure-free	worse
Simple partial			2
Complex partial	2	1	2
Absences		3	2
GTCS			1
Myoclonias	1	1	
Total	3	5	7

Table 5.2: Effect of lamotrigine on seizure frequency compared to placebo

Adverse events were evaluated for 59 patients after exclusion of the two patients who were withdrawn in the single blind baseline phase. Apparent treatment related adverse events were observed in 23 of 59 patients (39%) during the lamotrigine phase and in 19 of 52 patients (37%) in the placebo phase (Table 5.3). Adverse events led to withdrawal from the study of six patients (one in placebo phase): in five due to a rash and in one due to dizziness and nausea. The latter was later found to have a high phenytoin level of 31.7 μg/ml. Of the seven children who developed a rash during the lamotrigine phase, three were on sodium valproate, two on carbamazepine and two on no other antiepileptic drugs. The rash was mild without

involvement of the mucous membranes in all but one patient (co-medication: sodium valproate) who developed a high temperature and involvement of mucous membranes. Full blood count and liver function in this patient were normal. The study medication was stopped and the symptoms disappeared within three days. In one patient the study medication was reduced from 300 mg per day to 200 mg per day because of persistent headaches. All other adverse events were mild and transient.

	Number of patients (%)	
Adverse Event	**Lamotrigine (n=59)**	**Placebo (n=52)**
Cold or viral illness	9 (15)	9 (17)
Rash	7 (12)	2 (4)
Nausea	5 (8)	2 (4)
Injury or accident	4 (7)	0
Pharyngitis	4 (7)	1 (2)
Headache	1 (2)	2 (4)
Dizziness	0	2 (4)
Abdominal pain	0	2 (4)
Patients withdrawn	6 (10)	0

Table 5.3: Most frequently reported drug related adverse events

Adverse events reported by three or more patients in either phase are listed. Some patients reported more than one adverse event. Patients who withdrew during single-blind placebo phase are not included.

5.4.2. EEG findings

All 61 children had an initial ambulatory EEG recording, 50 children had two and 48 had three ambulatory EEG recordings. The mean duration of the recording at baseline was 18.15 hours (SD ±4.67), 16.80 hours (SD ±5.29) on placebo, and 16.73 hours (SD ±4.97) on lamotrigine.

In the initial ambulatory EEG recording 19 (31%) children had no discharges and 42 (69%) had discharges during the eyes open phase. In children with discharges the median number of discharges was 3.85/hr (range 0.6 to 115.6/hr, SD 24.68) and the median duration of discharges was 4.75 sec/hr (range 1.0 to 140.8 sec/hr, SD 33.78). These discharges were generalised in 11 patients, focal in 12 (right sided in seven, left sided in three and bilateral in seven) and both focal and generalised in 15 patients (with focal discharges right sided in seven, left sided in three and bilateral in four). There was a high correlation between frequency and duration of discharges (Pearson's Correlation Coefficient $r=0.887$; $n=61$; $p<0.001$).

As expected, neither the frequency nor duration of discharges were normally distributed. Figure 5.2 a) and b) demonstrates this for discharges at baseline, this was similar for discharges at placebo and lamotrigine. After data values of 0.0 set to 0.01 log [ln] transformation of the EEG data was performed. This resulted in a near normal distribution of the frequency and duration of discharges for the patients having discharges. Inclusion of children without discharges still resulted in a skewed distribution (Fig. 5.3 a) and b) for discharges at baseline). Thus, where statistics were applied to the whole group non-parametric tests were used.

Looking at individual patients, ten out of 48 patients (21%) completing the study had no discharges at either phase, 21 (44%) had a reduction of frequency of discharges, 8 (17%) had no change and 9 (19%) had an increase of discharges frequency.

Twenty-three (48%) patients had a reduced duration of epileptiform discharges whilst 25 (52%) patients either had no change or an increase of discharge duration (including 10 patients without discharges in either lamotrigine or placebo phase).

There was a considerable spontaneous variation in both the number of discharges per hour and the duration of discharges per hour (Fig. 5.4 a) and b)). This was true for both, individual and intraindividual variations.

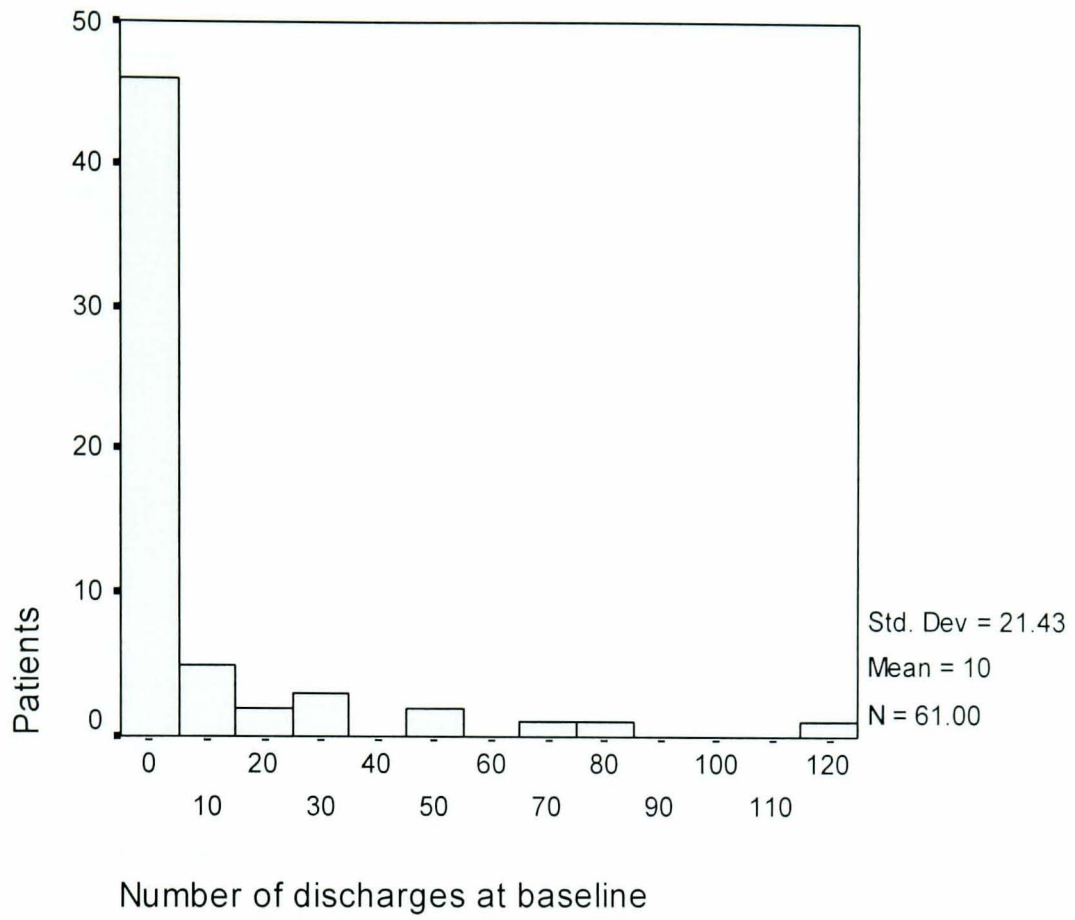


Figure 5.2 a): Distribution of frequency of discharges at baseline

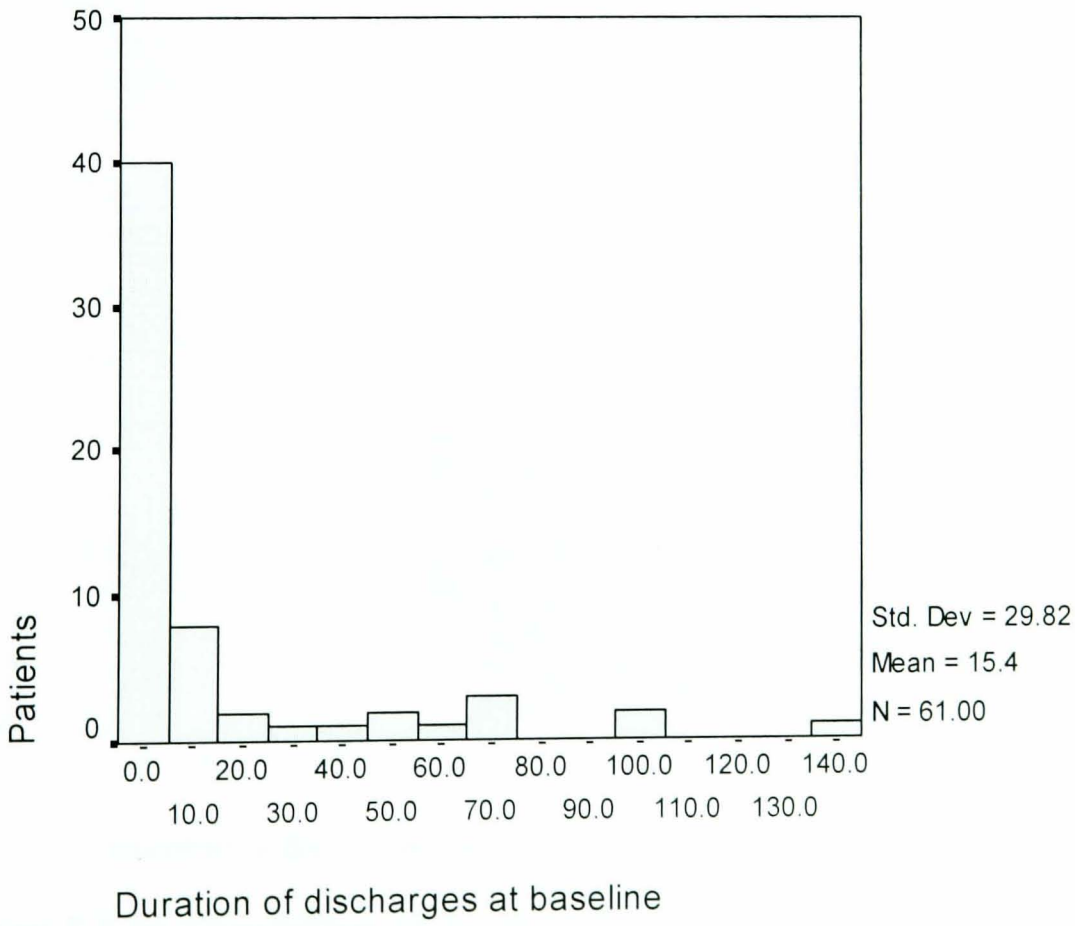


Figure 5.2 b): Distribution of duration of discharges at baseline

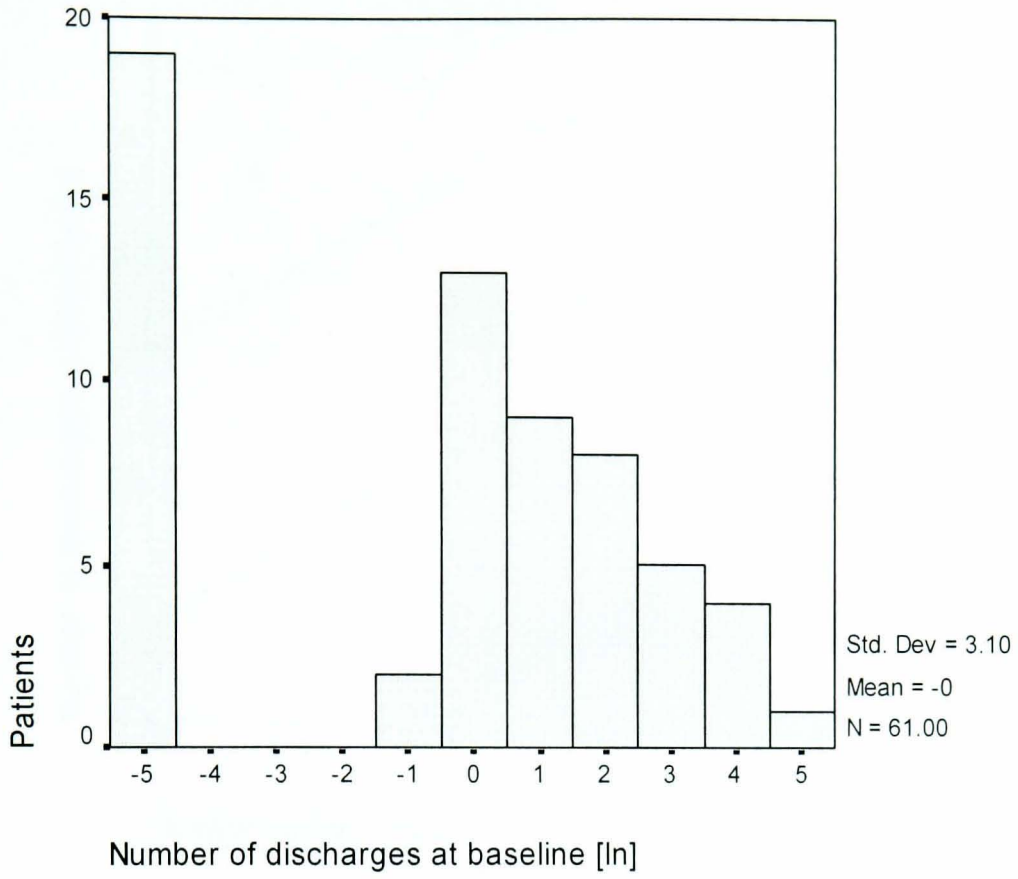


Figure 5.3 a): Distribution of frequency of discharges at baseline after data values of 0.0 set to 0.01 and log transformation.

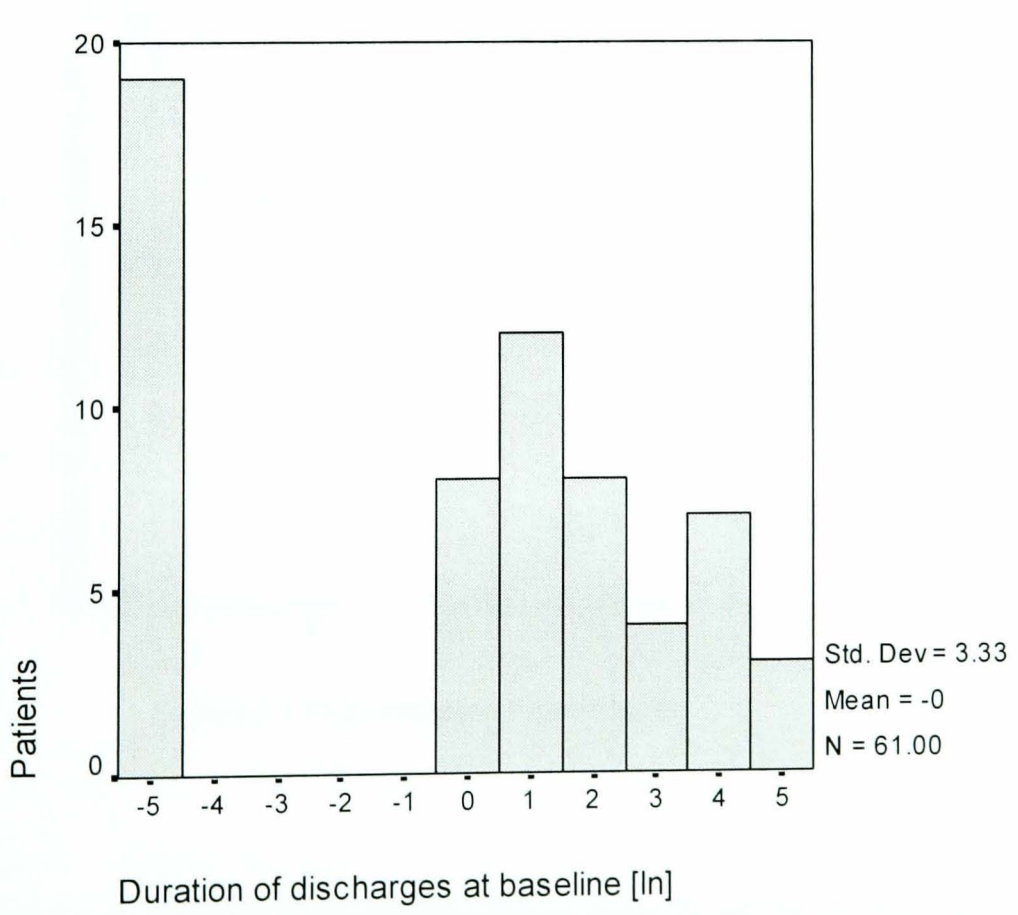
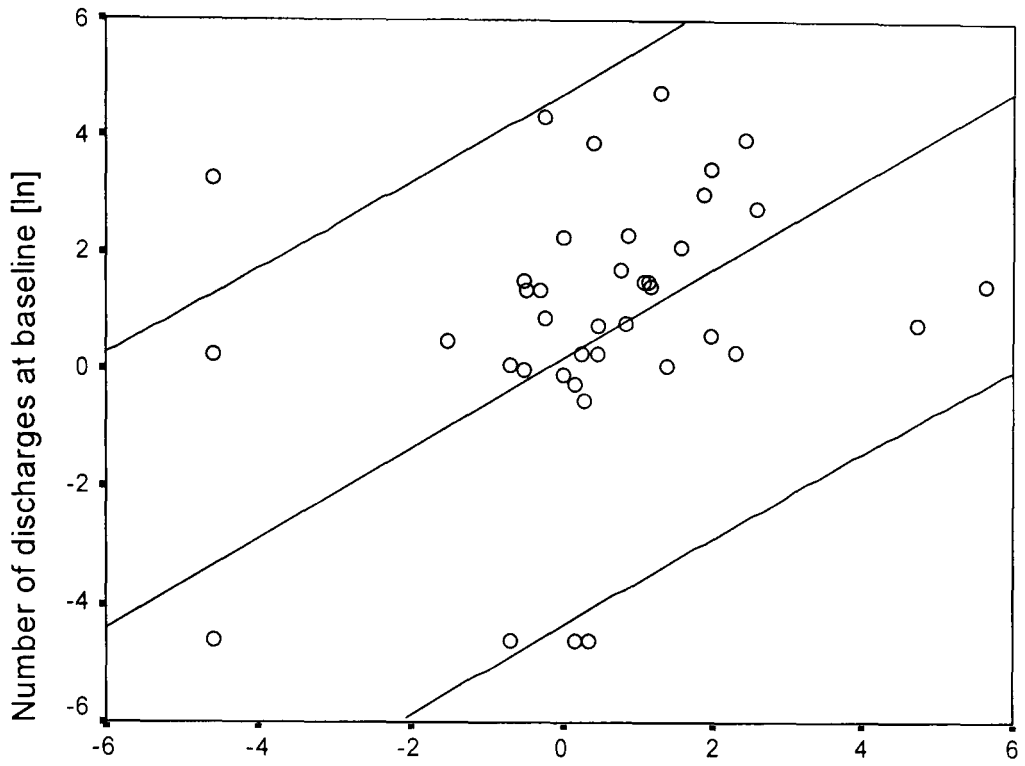


Figure 5.3 b): Distribution of duration of discharges at baseline after data values of 0.0 set to 0.01 and log transformation.

a)



b)

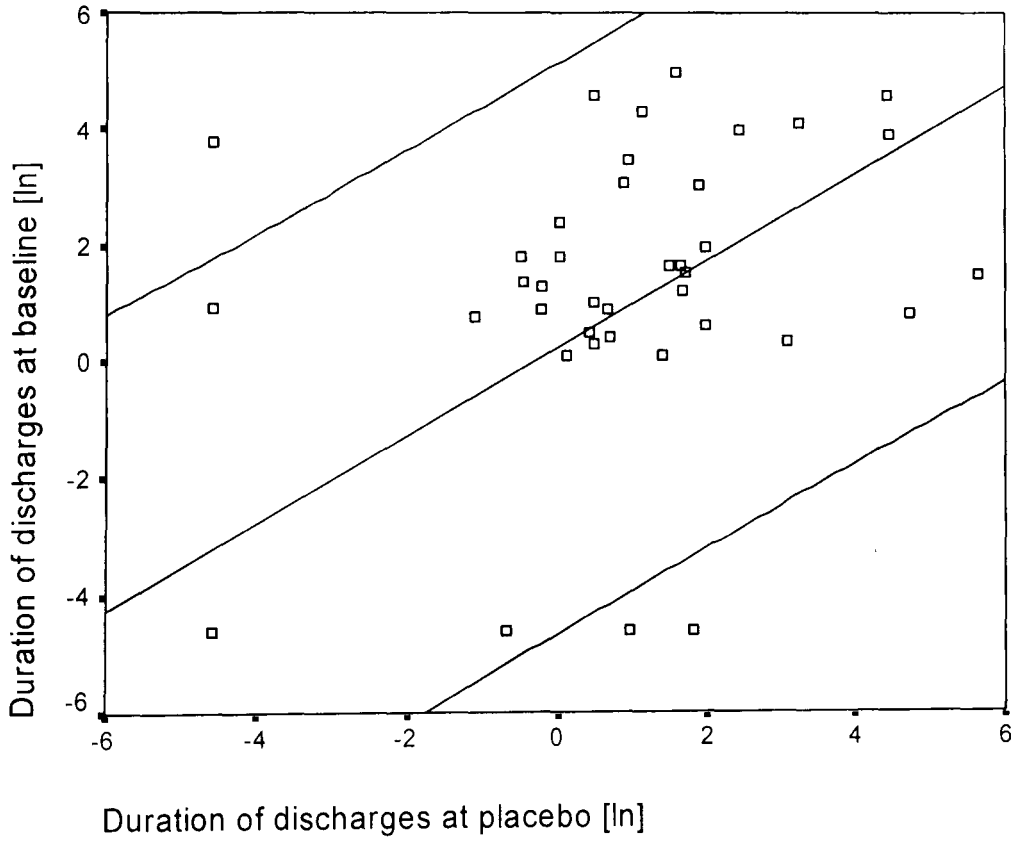


Figure 5.4: (a) Duration and (b) frequency of discharges in ambulatory EEG recordings at baseline and placebo. Data after values of 0.0 set to 0.001 and log transformation. Lines estimated 95% confidence regions.

Frequency and duration varied more within than between subjects. The variation was greater for patients with frequent discharges compared to patients with few discharges. Both the number of discharges per hour and the duration of discharges per hour were higher at baseline compared to placebo, but this difference was not significant (discharge frequency: z= -1.418; ns and discharge duration: z= -1.005; ns) (Table 5.4). Although the first ambulatory (at baseline) recording showed most discharges, subsequent recordings showed no order effect.

	Baseline	Placebo	Lamotrigine
Total number of patients	61	50	48
No. of patients with discharges	42 (69%)	36 (72%)	32 (67%)
Median number/hr (±SD)	3.9 (±24.7)	1.6 (±49.7)	1.8 (±26.7)
Wilcoxon Ranks Test*		ns	ns
Median duration sec/hr (±SD)	4.8 (±33.8)	2.8 (±52.0)	1.8 (±40.9)
Wilcoxon Ranks Test*		ns	**p < 0.05**

Table 5.4: Interictal discharges at baseline and after each treatment phase

*Comparison was done on all patients by means of percentage changes rather than absolute changes in that data were log transformed before analysis after values of 0.0 were changed to 0.001.

There was a statistically significant reduction of the duration of discharges in seconds per hour during lamotrigine treatment compared to placebo (z = -2.231; $p<0.05$), but not of the number of discharges per hour (z= -1.308, ns) (Table 5.4). Generalised and focal discharges were equally reduced by lamotrigine. Figure 5.5 summaries the type of discharges and the response to lamotrigine.

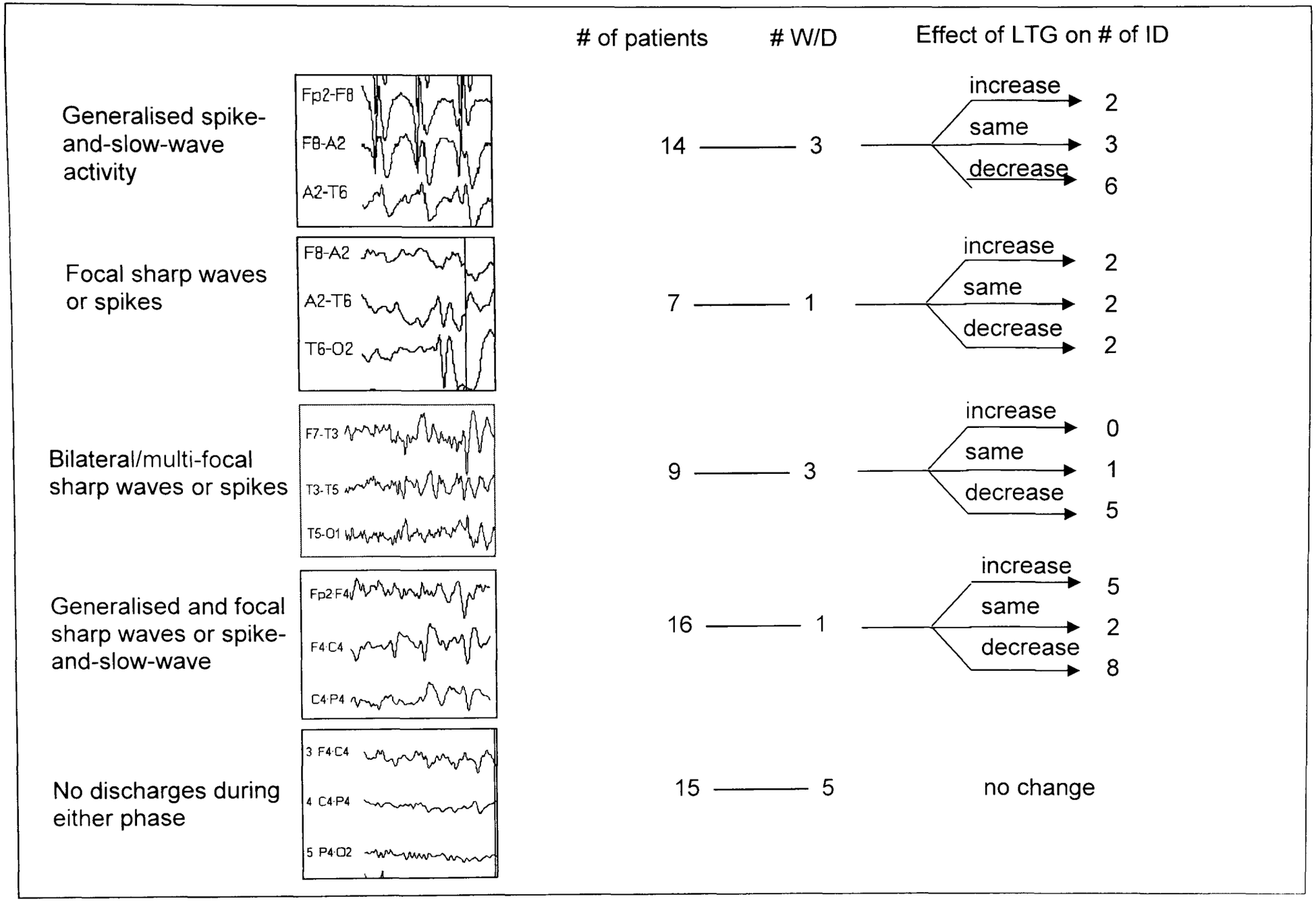


Figure 5.5: EEG findings at placebo and response to active treatment

The effect on discharges was independent of the type of epilepsy: 7 out of 13 (54%) patients with idiopathic partial epilepsy, 6 out of 14 (43%) idiopathic generalised epilepsy and 8 out of 21 (38%) with symptomatic partial epilepsy had a reduction of interictal discharges (χ^2=0.816; df=2; ns). Eleven patients had no discharges during either the placebo or the lamotrigine phase. Five patients had a 100% reduction of discharges on lamotrigine, whereas two patients had interictal discharges during the lamotrigine phase but not during the placebo phase.

There was a significant difference in the effect of lamotrigine on interictal discharges in patients with or without seizures. Of the 21 children with seizures during the study, 13 (62%) had a reduction of both frequency and duration of discharges. In contrast, of the 27 seizure-free children only 8 (30%) had a reduction of frequency of interictal discharges (χ^2=5.00; df=1; $p<0.05$) and 10 (37%) had a reduction of duration of interictal discharges (χ^2=2.93; df=1; $p<0.1$). There was no correlation between the effect of lamotrigine on discharges and the number of seizures during the study. As the number of patients with a reduction of seizures of more than 50% on lamotrigine compared to placebo was too small (n=7) no correlation between reduction of seizures and reduction of interictal discharges was possible.

5.5. Discussion

Our group of patients with well-controlled epilepsy appear in many respects to be typical of the population of school-age children with epilepsy: 40% symptomatic epilepsies, 25% idiopathic partial epilepsies and 30% idiopathic generalised epilepsies (Cavazzuti, 1980). As expected there were more boys than girls and the IQ was within normal range but somewhat below average (Rodin, 1989).

The quantification of discharge frequency can be done either visually or by automated analysis. The difficulty of the latter, even if using the more recent models, lies in differentiating true cerebral activity from muscle activity and other artefacts. Visual analysis is obviously very laborious and time consuming, but is more accurate and reliable,

particularly if the discharge rate is low. As our study involved only 61 patients and some of them had no discharges we opted for the latter method.

Conflicting results in studies on EEG abnormalities in patients with epilepsy may be explained by the fluctuating nature of interictal discharges. The rate and extent of interictal discharges can vary considerably from one moment to the next or from one day to the next. A random 20 minutes EEG recording samples only a small fraction of the activity that may occur during an entire day (Stevens et al., 1972). The results of our study show that the day-to-day variability of interictal discharges is considerable even in children with mild or well-controlled epilepsy and prolonged EEG recordings are essential to evaluate the effect of a drug on interictal discharges. This confirms the findings in adults with active epilepsy (Martins da Silva et al., 1984; Burr and Stefan, 1987; Mayr et al., 1989).

The frequency and duration of discharges per hour were higher during the baseline than the placebo recording. Although most conditions like time of the day, weekday, examination room and people involved were constant, it was unavoidable that the children were excited or anxious before they had the first ambulatory recording. Their sleep therefore may have been disturbed before or during the recording. Sleep deprivation causing drowsiness during the daytime is known to enhance the frequency of discharges in patients with epilepsy (Mattson et al., 1965; Veldhuizen et al., 1983). Anxiety or other causes of arousal itself suppress interictal discharges in most patients, but may enhance them in some (Rugland, 1990). These effects may be diminished by the familiarisation with the study procedures. Yet we found no order effect with fewer discharges between the second and third EEG recordings. This could mean that, after dealing with the uncertainties of the first EEG, the subsequent EEGs were much less affected by the factors described above giving a more reliable picture of actual amount of discharges. This has implications for future studies, particular AED studies, insofar that children should be familiarised with the EEG/ambulatory recordings before the actual study data are ascertained as has been done here.

The overall tolerance for lamotrigine was good with numbers of reported side effects similar to other studies (Culy and Goa, 2000; Messenheimer et al., 2000). As expected the most common side effect was a drug rash in seven patients during the lamotrigine phase. This rash led to withdrawal in five patients. This is a relatively high incidence compared to newer studies is be explained by the faster introduction of lamotrigine in our study, in

accordance with the recommendations at the time. The recommended dose titration has since been slowed which has decreased the incidence of rash (Wong et al., 1999).

Lamotrigine reduced significantly the duration of discharges per hour, but not the total number per hour. However, these figures include ten patients with no interictal discharges at any time of the study. This is in contrast to other studies, where the effect of lamotrigine on discharge frequency was considerable. Binnie et al. (Binnie et al., 1986) reported a reduction of 78-98% in discharge rate following a single oral dose of lamotrigine and a marked reduction in response to photic stimulation. Seven out of ten patients had a reduction of discharges during a seven-day administration of lamotrigine in a double-blind placebo-controlled study (Binnie et al., 1987). Using an ambulatory spike and wave monitor Besag (1994) evaluated the effect of lamotrigine on spike and wave discharges in 17 children and adolescents with epilepsy. There was a marked reduction of discharges of more than 80% compared with baseline in eight patients. These findings in patients with on-going epilepsy have been confirmed by others (Chevalier et al., 1995; Marciani et al., 1996).

One explanation for the conflicting results on the effect of lamotrigine on discharges arises from different study designs. As discussed above baseline recordings show more discharges than subsequent recordings. If discharge frequency under lamotrigine were compared to a baseline recording (Besag, 1994; Marciani et al., 1996) part of the effect might be due to the familiarisation of the patients to the procedures rather an effect of the drug. The intra-patient variability of interictal discharge frequency further complicates the assessment of AED effects. This is particularly important in patients who have few discharges in whom drug effects are difficult to demonstrate. Furthermore, the numbers of patient in most of the above mentioned studies were small. More importantly, in all these studies patients had active, usually severe epilepsy and frequent discharges. Our results suggest that the effect of lamotrigine on interictal discharges differs in patients with uncontrolled seizures.

Besag found no association between the reduction of discharges and the reduction of overt seizures (Besag, 1994). In our study the number of patients with a 50% seizure reduction on lamotrigine was too small for statistical analysis. More recently, a double blind, placebo-controlled, cross-over study on the effect of lamotrigine on interictal discharges in children with drug-resistant epilepsy has been published (Eriksson et al., 2001). Twelve

patients aged 4-12 years, most of them with Lennox-Gastaut syndrome, had 24-hour telemetry EEG recordings during baseline, placebo and lamotrigine phases. Similar to our results only the duration not the frequency of discharges was significantly reduced. Ten of 12 patients showed a reduction of duration of interictal discharges on lamotrigine by a mean of 81%. It is also important to note, that these patents were recruited from a larger group of patients who had responded to lamotrigine with a reduction of seizures or improvement of behaviour. They also noted that particularly long discharges of a duration of more than 30 seconds were significantly reduced, whereas shorter periods of discharges or single discharges were not affected. As none of our patents had discharges of this duration it is not surprising that the mean reduction in our group of patient was less.

Thus, it appears that in humans lamotrigine has an effect on the termination rather than on the initiation of discharges. This confirms the findings in animal studies which suggest that lamotrigine is a use dependent inhibitor of Na+ currents and thus acts on the slow inactivated state terminating interictal discharges (Xie et al., 1995).

In conclusion, inter- and intraindividual variations of discharges make it difficult to evaluate the effect of antiepileptic drug on discharges without prolonged EEG recordings. Lamotrigine has a moderate suppressive effect on interictal discharges in children who are seizure-free but may be more effective in reducing discharges in patients with ongoing seizures or drug resistant epilepsy.

Chapter 6: Effect of lamotrigine and interictal discharges on behaviour

6.1. Summary

Objective: It is generally agreed that children should be treated for epilepsy only if they have clinical seizures. The aim of this study was to examine whether suppressing interictal discharges affect behaviour in children with epilepsy.

Methods: In a double blind, placebo-controlled, cross-over study, 61 children with well-controlled or mild epilepsy were randomly assigned to add-on therapy with either lamotrigine followed by placebo or placebo followed by lamotrigine. Ambulatory EEG recordings and behavioural assessments were performed during baseline and at the end of placebo and drug phases. The null hypothesis was that lamotrigine would not affect behaviour in patients with a reduction of EEG discharges.

Results: Global rating of behaviour improved only in patients who showed a reduction in either frequency ($p<0.05$) or duration of discharges ($p<0.05$) during active treatment, but not in patients without a change in discharge rate. This improvement was mainly seen in patients with partial epilepsy ($p<0.005$).

Conclusion: Our data suggest that suppressing interictal discharges can improve behaviour in children with behavioural problems and epilepsy, particularly partial epilepsy. Focal discharges may be involved in the underlying mechanisms of behavioural problems in epilepsy.

6.2. *Introduction*

Children with epilepsy are at a higher risk of developing behavioural problems and psychiatric disorders than their healthy peers (Rutter et al., 1970) or than children with other chronic disease (Hoare, 1984). This is not only important for children with uncontrolled epilepsy and learning difficulties but also for that majority of children with epilepsy whose seizures respond well to antiepileptic drugs (AEDs) and who are educated in mainstream schools. Even those children have been found to have more learning and behavioural problems in school compared to matched controls and achieve less than expected for their age and IQ (Seidenberg et al., 1986; Aman et al., 1992).

Increased behavioural problems in children with epilepsy are a consequence of a number of interacting influences including underlying brain lesion, age of onset, AEDs, psychosocial issues, seizure type and frequency, and interictal EEG abnormalities (Kwan and Brodie, 2001; Hoare, 1984). See section 1.2.3.6 and 1.4 for more details. The only way to determine whether discharges cause cognitive and behavioural problems in children with epilepsy or are co-existent due to a common cause, is by determining whether cognition and behaviour improve when EEG discharges are suppressed. It is generally agreed by neurologists and paediatricians that patients should be treated for epilepsy only if they have clinical seizures. Treating the EEG, so called 'EEG cosmetics', is generally condemned.

In order to test this view a double-blind, placebo-controlled, cross-over trial was carried out to assess the effect of suppressing interictal discharges on behaviour in children with epilepsy. The null hypothesis was that suppression of discharges would not be associated with a change in behaviour. To avoid the confounding factor of changing seizure frequency on behaviour only patients were included who were seizure free or who had infrequent seizures. It was essential to exclude an independent psychotropic effect of the drug on behaviour and thus both patients with and without interictal discharges were included. Consequently it was possible to compare behavioural changes in patients with and without a reduction of interictal EEG discharges.

6.3. Methods

6.3.1. Patients

Patients were recruited from paediatric outpatient clinics at three study sites: Guy's Hospital, King's College Hospital and The National Centre for Young People with Epilepsy (NCYPE, former St Piers Lingfield), UK. Patients aged 7 to 17 years were eligible if they had a confident diagnosis of epilepsy and were seizure free or were having occasional seizures but in whom the responsible clinician or parent/careers felt that further adjustments to AEDs was not warranted. For more details on patient recruitment and inclusion criteria see chapter 3.5.

6.3.2. Procedure

This was a double blind, randomised, placebo-controlled, cross-over study with lamotrigine. See section 3.6 for study protocol (Figure 3.7 and Table 3.2) and dosage regime (Table 3.1).

6.3.3. Efficacy, Safety and Behaviour Assessments

See section 3.4 for assessment of interictal discharges and section 3.6 for safety assessment. The methodology of assessment of efficacy (suppression of ID), safety and behaviour has been outlined in sections 3.4, 3.6 and 3.2.1 respectively. As described in section 3.5 these assessment were carried out at entry to the trial and the end of each treatment phase – either lamotrigine or placebo.

6.3.4. Statistical analysis

Statistical methods for the discharge data are outlined in section 3.4 and 5.3. Changes in global rating of behaviour were analyzed by repeated measurement multivariate analysis of variance (ANCOVA) between treatment groups (lamotrigine and placebo), with response to lamotrigine as covariant (with or without reduction of subclinical epileptiform discharges number/duration). To identify the most relevant

behavioural subscale the univariate test was used. The following variables were considered as within-subject factors: order of randomization, occurrence of seizures, IQ and type of epilepsy. SPSS 10.0 for Windows was used for all statistical analyses. A p-value of <0.05 was considered significant. All statistical tests used were 2-tailed. Analysis was by intention to treat.

Changes in global rating of behaviour were analyzed by repeated measurement multivariate analysis of variance (ANCOVA) between treatment groups (lamotrigine and placebo), with response to lamotrigine as covariant (with or without reduction of discharges). To identify the most relevant behavioural subscale the univariate test was used. A p-value of <0.05 was considered significant. All statistical tests were 2-tailed. Analysis was by intention to treat.

6.4. Results

Of the 64 patients screened, 61 were enrolled in the study and randomly assigned to receive first lamotrigine and then placebo or vice versa (figure 5.1). Thirteen children were withdrawn from the study, including two children who did not enter the double-blind treatment phase. Eight of these children had discharges. Patients in both groups had similar demographics and baseline characteristics (table 5.1).

Details on seizure frequency and results of ambulatory EEG recordings see chapter 5.

The effect of lamotrigine on seizures and ID is detailed in chapter 5.

In summary twenty-one (44%) patients had a reduced frequency of discharges, whilst 16 (33%) patients either had no change or an increase in the frequency of discharges and 11 (23) patients had no discharges during either lamotrigine or placebo phase. Twenty-three (48%) patients had a reduced duration of discharges whilst 14 (29%) patients either had no change or an increase of discharge duration and 11 (23%) patients had no discharges in either lamotrigine or placebo phase. The effect of lamotrigine on discharges was similar across the types of epilepsies.

The mean behavioural scores at baseline as assessed by both parents and teachers for the whole group were all within the normal range (50 ± 1 SD) (table 6.1). Taking

scores of more than two SD above the mean as abnormal in individual patients(the higher the score, the more disturbed the behaviour), 13 (22%) had at least one abnormal score in the parental assessment and 20 patients (33%) had at least one abnormal score in the teachers' assessment (Table 6.1).

	Mean	SD	Patients with scores +2SD (%)
Parents scale			
Antisocial	42.28	5.78	0
Anxious/shy	52.02	12.15	6 (10)
Conduct disorder	48.38	10.50	5 (8)
Hyperactive/immature	47.75	10.08	4 (7)
Learning problem	47.65	9.17	2 (3)
Obsessive compulsive	50.85	10.95	5 (8)
Psychosomatic	51.63	9.13	3 (5)
Restless/disorganized	52.98	10.25	3 (5)
Teachers scale			
Asocial	53.53	13.20	6 (10)
Anxious passive	53.72	10.13	5 (8)
Conduct problem	51.60	10.70	4 (7)
Daydream/attention	57.40	13.23	13 (22)
Emotional/indulgence	54.60	12.09	7 (12)
Hyperactivity	52.65	9.74	5 (8)

Table 6.1: Behavioural scores at baseline

	Frequency of interictal discharges					Duration of interictal discharges				
	With reduction		Without reduction			With reduction		Without reduction		
	Mean	SD	Mean	SD	F	Mean	SD	Mean	SD	F
Global score	**-1.34**	**4.56**	**.47**	**3.48**	***2.17****	**-1.16**	**4.49**	**.39**	**3.54**	***2.50****
Parental sub-scores										
Antisocial	-2.72	4.96	-0.18	4.17	.33	-2.58	4.86	-0.19	4.27	0.01
Anxious	-1.44	7.36	0.05	4.66	.01	-1.47	7.15	0.14	4.76	0.12
Conduct disorder	-3.39	6.35	-1.36	4.23	5.67*	-2.74	6.80	-1.86	3.62	4.39*
Hyperactive	-2.00	6.24	-0.82	5.61	.97	-1.68	6.22	-1.05	5.64	0.69
Learning problem	-1.39	7.16	-0.23	3.65	2.86	-0.89	7.29	-0.62	3.23	2.43
Obsessive	0	6.42	0.45	5.54	2.80	0.53	6.64	0.00	5.24	2.83
Psychosomatic	-2.78	10.25	-0.45	6.59	2.94	-3.53	10.48	0.33	5.59	4.40*
Restless	-2.61	4.12	-1.77	6.88	.01	-2.58	4.00	-1.76	7.05	0.01

Values shown are calculated by subtracting the score during placebo phase from the corresponding score during lamotrigine phase so that a negative score reflects an improvement in behaviour and a positive score a worsening. * $p<0.05$

Table 6.2 a) Observed changes in global score as well as parental behavioural subscale T-scores during placebo and lamotrigine phases comparing patients with and without a reduction of interictal discharges on lamotrigine: Only patients with a reduction of ID showed an improvement of the global behavioural score.

	Frequency of interictal discharges					Duration of interictal discharges				
	With reduction		Without reduction			With reduction		Without reduction		
	Mean	SD	Mean	SD	F	Mean	SD	Mean	SD	F
Teacher sub-scores										
Asocial	1.67	4.63	0.82	9.74	0.67	1.32	4.75	1.10	9.89	0.57
Anxious passive	1.00	4.16	0.95	6.61	2.52	0.53	4.54	1.38	6.45	2.76
Conduct problem	-1.44	11.43	1.32	6.42	1.82	-0.79	11.47	0.86	6.19	1.22
Daydream	-1.00	9.49	2.27	8.11	0.01	-0.95	9.22	2.38	8.29	0.07
Emotional	-2.06	12.14	2.64	8.14	1.33	-1.42	12.12	2.29	8.17	0.55
Hyperactivity	-2.00	10.57	0.86	6.16	1.61	-1.42	10.58	0.48	6.03	0.98

Values shown are calculated by subtracting the score during placebo phase from the corresponding score during lamotrigine phase so that a negative score reflects an improvement in behaviour and a positive score a worsening.

Table 6.2 b): Observed changes in teachers' behavioural subscale T-scores during placebo and lamotrigine phases comparing patients with and without a reduction of interictal discharges on lamotrigine: patients with a reduction of ID showed an improvement of the global behavioural score.

Whilst there was no difference in global rating of behaviour (combining parents' and teachers' scale) when comparing placebo and lamotrigine for the total group of patients (ANCOVA: F=0.79; df=14; ns), there was a significant improvement in global rating of behaviour in the children who showed a reduction of discharges during the lamotrigine phase (ANCOVA: frequency of discharges: F=2.17; df=14; $p<0.05$; duration of discharges: F=2.50; df=14; $p<0.05$).

This improvement was seen across all parental subscales (range of mean difference for parental scale 0 to –3.9) and in 4 out of 6 subscales in the teachers' scale (range of mean difference for teachers' scale +1.2 to –3.4). It was significant for the parental conduct disorder subscale ($p<0.05$) and parental psychosomatic subscale ($p<0.05$) (table 6.1 a and b). None of the teachers' subscales individually showed a significant difference in the univariate test.

	df	F	p value
Placebo-Lamotrigine	14	0.788	ns
Placebo-Lamotrigine discharge number	14	2.168	<0.05
Placebo-Lamotrigine discharge duration	14	2.502	<0.05
Placebo-Lamotrigine randomisation	14	0.787	ns
Placebo-Lamotrigine seizures	14	1.087	ns
Placebo-Lamotrigine IQ	14	0.704	ns
Placebo-Lamotrigine type of epilepsy	14	1.128	ns

Table 6.3: ANCOVA: Difference between groups and effect of covariates and within-subject factors

This effect depended largely on whether patients had a partial or generalized epilepsy (ANCOVA: F=3.53; df=14; $p<0.005$). Patients with partial epilepsy were more likely to show an improvement of behaviour when discharges were suppressed whereas a change of behavioural rating in patients with generalized epilepsy was independent of the effect on discharges. There was no difference between idiopathic partial epilepsy and symptomatic partial epilepsy.

A similar difference was seen depending on which drug the patient was on (ANCOVA: $F=2.78$; $df=28$; $p<0.001$). Patients with carbamazepine were more likely to have an improvement of behaviour if discharges were suppressed than patients with sodium valproate or other drugs. However, patients with partial epilepsy showed a similar effect whether on carbamazepine or on other drugs. There was no order effect due to randomization (ANCOVA: $F=1.01$; $df=14$; ns) nor presence of seizures (ANCOVA: $F=0.26$; $df=14$; ns). A sub-analysis of children without seizures at baseline ($n=35$) showed the same trends in the behavioural scales and similar results in the general linear modelling: a significant change in the global rating of behaviour during active treatment for patients with a reduction in frequency of discharges (ANCOVA: frequency of discharges: $F=4.16$; $df=14$; $p<0.05$) or duration of discharges ($F=4.82$; $df=14$; $p<0.01$). Table 6.2 summarises the results of the ANCOVA.

6.5. Discussion

In this study suppression of interictal discharges was associated with improved global rating of behaviour in children with behavioural problems and well-controlled epilepsy. This is the first study to present such evidence in patients with epilepsy under controlled conditions. The controlled study design with standardized behavioural questionnaires and an appropriate number of patients avoided methodological pitfalls as recently discussed (Kwan and Brodie, 2001).

Single observations and uncontrolled reports have claimed an improvement of cognitive functioning by suppressing discharges with AEDs in patients with epilepsy (Rugland, 1990; Aarts et al., 1984). Our group has previously performed a preliminary study using sodium valproate or clobazam add-on to suppress discharges in ten children with uncontrolled epilepsy. A reduction of discharge rate was associated with improvement in global rating of psychosocial function in eight out of ten children (Marston et al., 1993). However, all but one patient showed an unexpected reduction in seizure frequency on active treatment thereby making it difficult to interpret the results. To remove this confounding factor in the present trial

only patients were included who were either seizure free or were having few seizures. There were no significant differences between patients with and without seizures. In clinical practice, occasional seizures are not considered to represent any substantial seizure burden and these patients are often regarded as well controlled. Generalized spike-and-slow-wave discharges may be accompanied by subtle clinical changes (TCI) as demonstrated on close assessment including psychological monitoring (Binnie, 2003). To exclude these children would involve ignoring a major group of subjects who might benefit from the treatment proposed. Even though all patients had a degree of behavioural and/or cognitive dysfunction reported by parents, this was not reflected by the baseline scores of the total group of patients. Nevertheless, due to the design of the study the conclusions necessarily apply to children with some concern about learning or behaviour. They can not be taken to apply to children about whom no such concerns are expressed. Nevertheless, it is the case where the concerns are expressed or not depends upon the norms and expectations of parents and teachers – which may vary.

In clinical research, behavioural scales, such as the Conner Rating scale or the Achenbach Child Behaviour Checklist, are often employed to compare t-score before and after intervention quantitatively rather than qualitatively defining what is a normal or abnormal score (Aman et al., 1992; Weglage et al., 1997; Stores et al., 1998). This may obtain a significant result which may or may not be clinically relevant, but this problem is inherent to all research using behavioural scales in children with mild problems.

My findings are in contrast to a recent study in eight children with learning and behavioural problems whose behaviour did not improve on active treatment with sodium valproate (Ronen et al., 2000). However, only four patients had a reduction of discharges and more importantly no separate analysis was performed for patients with and without reduction of discharges.

It was mainly patients with partial epilepsy who benefited from discharges suppression. In this study lamotrigine had a similar effect on discharges in both partial and generalized epilepsy. Although more patients with idiopathic partial epilepsy had frequent discharges, many patients with symptomatic partial epilepsy

had no discharges or a low discharge frequency, making a relationship between baseline discharge frequency and magnitude of rating change unlikely.

Patients on carbamazepine were also more likely to show an improvement in behaviour when discharges were suppressed compared to patients on other drugs. This was due to the choice of first line AEDs in partial and generalized epilepsy rather than due to an independent effect as carbamazepine is not associated with the improvement in partial epilepsy. It remains unclear whether the combination of lamotrigine and sodium valproate may cause more behavioural dysfunction than other combinations. It is well established that AED polytherapy itself is a risk for behavioural dysfunction in children with epilepsy (Bourgeois, 1998). By adding another drug into the current regime of our patients it is possible that behavioural problems were accentuated in some. Nevertheless, there was a significant behavioural improvement in the lamotrigine group in the patients with a reduction of discharges.

Lamotrigine is one of the few AEDs, which suppresses discharges (Besag, 1994; Eriksson et al., 2001). It does not appear to affect cognition adversely in patients with epilepsy (Besag, 1995; Meador and Baker, 1997). In a recent study low dose lamotrigine had a positive effect on reaction time measurements and on one out of six mood scales in healthy volunteers. However the number of volunteers tested was small (Aldenkamp et al., 2002). Furthermore, several uncontrolled studies reported improved cognition and behaviour (Gibbs et al., 1992; Uvebrant and Bauziene, 1994; Besag, 1994; Buchanan, 1995). In a double blind adjunctive study primarily in children with Lennox-Gastaut syndrome and uncontrolled epilepsy significant behavioural improvement and increased alertness were noted in all 17 "respondern" (>50% seizure reduction) during active treatment (Erikson et al., 1998). This improvement was apparently unrelated to seizure control.

An overall effect of lamotrigine could not be confirmed but rather an indirect effect via suppression of interictal discharges. The changes on the behavioural scale seen in our patients cannot be attributed to drug effects alone as they are confined to those subjects who showed a reduction of epileptiform activity on lamotrigine, and were not seen in those who showed no reduction or had no discharges.

In psychiatry, LTG is used for the treatment of depression (Ketter et al., 1999) for its anergic profiles, e.g., for the treatment of depression, apathy, and hypersomnia. Their assumed effect is cognitive activation. Mood improvements have been reported in several open clinical studies in epilepsy patients (Smith et al., 1993; Brodie et al., 1995; Schapel and Chadwick 1996; Besag, 2000). In a controlled trial of interictal depression, LTG monotherapy was associated with earlier and larger improvement compared with valproate monotherapy (Edwards et al., 2001). Recently it has been suggested that LTG also has a broad spectrum efficacy in bipolar disorder (Calabrese et al., 1998). In a controlled study it was well-tolerated and had a similar effect to lithium, particularly for prophylaxis of depression (Calabrese et al., 2003). The reported effects of quality of life and behaviour may be partially related to and explained by these mood effects.

How are interictal discharges and psychosocial disturbances related? Interictal discharges and behavioural problems could both be caused by an underlying pathology, and thus be co-existing but independent phenomena. However, in this cross-over study the patients acted as their own controls and only those with a reduction in discharges showed an improvement of behaviour. Interictal discharges may cause fragmented sleep, a well recognized cause of cognitive and behavioural problems (Stores et al., 1998; Cortesi et al., 1999). In a recent study using lamotrigine no improvement of nocturnal discharges or neuropsychological function could be found (Placidi et al., 2000). Finally, interictal discharges may cause psychosocial disturbances by directly interacting with cognitive and behavioural function. Using EEG-linked cognitive tests, TCI has been found in 50% of patients with sufficient discharges (Binnie and Marston, 1992). Generalized bursts lasting at least 3 seconds are most likely to produce demonstrable TCI, but they are also found during briefer and focal discharges (Aarts et al., 1984; Shewmon and Erwin, 1988). TCI may impair day-to-day psychosocial function (Marston et al., 1993). It is well established that children with focal EEG abnormalities and/or complex partial seizures are particularly vulnerable to psychiatric and behavioural disturbance (Bagley, 1973; Hoare, 1984; Weglage et al., 1997). Our results provide evidence for the first time that particularly focal discharges may play a role in the underlying mechanisms of behavioural problems.

Chapter 7: Effect of lamotrigine on cognition

7.1. Summary

Objective: There is evidence that lamotrigine does affect cognition in healthy volunteers or adults with epilepsy. This chapter addresses cognitive effects of lamotrigine in children with epilepsy.

Method: In a double blind, placebo-controlled, cross-over study, 61 children with well-controlled or mild epilepsy were randomly assigned to add-on therapy with either lamotrigine followed by placebo or placebo followed by lamotrigine. Each treatment phase was 8 weeks, the cross-over period 6 weeks. A cognitive test battery was performed during EEG monitoring at baseline and at the end of placebo and drug phases. The paired student t-test was used for statistical analysis (2-ided) with a p-value of 0.01 considered significant.

Results: We found no significant difference in continuous performance, binary choice reaction time, verbal and non-verbal recognition, computerised visual searching task, verbal and spatial delayed recognition and verbal and non-verbal working memory between placebo and lamotrigine treatment phase. Results were not influenced by the reduction of interictal discharges during active treatment.

Conclusion: Results of this study suggest for the first time in a controlled manner that lamotrigine in the usually recommended doses has no significant cognitive effects in children.

7.2. Introduction

There is evidence that AED treatment has a greater impact on cognitive function and behaviour than previously suspected. Bennet and Stores (1984) showed that children receiving any antiepileptic drug had impaired concentration and poorer processing ability, and were less alert than those receiving no treatment. Cognition, defined as the ability to acquire, retain, process and act upon information, depends on many factors in the person's overall physical and mental state (e.g. pain, arousal, sensation and emotion). AEDs can act on all of these factors and thereby indirectly affect the cognitive process.

The following cognitive domains have been established as particularly vulnerable in patients with epilepsy: speed of information processing, memory, alertness, sustained and focused attention, and motor fluency. Some studies also mention language and problem solving (Aldenkamp et al., 1987, 1990).

There are over 100 studies looking at the cognitive side effects of AEDs, most of them in adults. Nevertheless there is still much uncertainty because of methodical shortcomings in most studies. These include: small sample size, short observation period, open label studies, no or inappropriate controls, no or inadequate randomisation and inappropriate statistical methods (Devinsky, 1995; Kwan and Brodie, 2001; Brunbech and Sabers, 2002; Loring and Meador, 2004). The situation is even more uncertain in children with epilepsy (Loring and Meador et al., 2004) although studies in rats have demonstrated potentially serious effects of AEDs on the developing brain, including apoptotic neurodegeneration (Olney et al., 2002). Even modest cognitive side effects in children may have significant consequences because they can influence learning of new skills and the ability to develop social strategies. There is convincing evidence that phenobarbitone has a negative effect on IQ in children with epilepsy (Farwell et al., 1990, 1992) which appears to have a long-term effect on academic achievement even after drug withdrawal (Wolf et al., 1981). The effects of other established AEDs in children are largely unclear due to the above mentioned methodical problems. Cognitive impairment is likely to occur with phenytoin and clonazepam, but is less evident with sodium valproate, and carbamazepine. Further, there are very few studies of the more recently introduced AEDs in children using formal testing (Loring and Meador, 2004).

Studies in adults and children suggest that lamotrigine is better tolerated than most long-established antiepileptic drugs. Sedation and other CNS side effects in particular are less common and quality-of-life studies suggest that it has comparatively few cognitive side effects (Steiner et al., 1999; Gillham et al., 2000; Jacoby et al., 1996). However, only limited data exists on formal cognitive test performances in adults. Meador et al. (2001) examined the effect of lamotrigine on healthy volunteers. They assessed cognitive and behavioural effects of carbamazepine and lamotrigine in 25 healthy adults using a double-blind, randomized crossover design with two 10-week treatment periods avoiding many of the above problems. Direct comparison of the two AEDs revealed significantly better performance on 19 (48%) variables for lamotrigine but no changes for carbamazepine. Differences spanned both objective cognitive and subjective behavioural measures, including cognitive speed, memory, mood factors, sedation, perception of cognitive performance, and other quality-of-life perceptions. Comparison of lamotrigine with non-drug average (placebo) revealed better performance on one (2.5%) variable for non-drug average and on one (2.5%) variable for lamotrigine. The authors concluded that in contrast to carbamazepine, lamotrigine produces no adverse cognitive and behavioural effects in healthy volunteers. They did not interpret the better performance of lamotrigine in one variable compared to placebo as evidence for a positive effect of lamotrigine on cognition as it was only one out of 19 variables. Similar results were found by others (see section 1.1.3.5 for the following studies: Martin et al., 1999; Aldenkamp et al., 2002).

In a randomised, placebo-controlled, double-blind, cross-over, add-on study of lamotrigine in adult patients with refractory epilepsy, 54 patients completed a small cognitive test battery including three tests of concentration and psychomotor performance (Smith et al., 1993). The lamotrigine dosage was 400 mg/day (patients receiving enzyme-inducing drugs only) or 200 mg/day (patients receiving an enzyme-inducing drug and valproic acid). Patients were tested at baseline and at the end of each treatment period with no significant difference between lamotrigine and placebo shown. The same result was found in a number of small studies in adult patients with epilepsy (Banks et al., 1991; Placidi et al., 2000).

There are open studies and single case reports in children suggesting that lamotrigine has a similar CNS profile in children. However, no randomised and controlled studies have been published so far. This is the first placebo controlled study on the cognitive effect of lamotrigine in children with epilepsy using formal neuropsychological testing.

7.3. Methods

7.3.1. Patients

Patients were recruited from pediatric outpatient clinics at three study sites: Guy's Hospital, King's College Hospital and The National Centre for Young People with Epilepsy (NCYPE, former St Piers Lingfield), UK. Patients aged 7 to 17 years were eligible if they had a confident diagnosis of epilepsy and were seizure free or were having occasional seizures but in whom the responsible clinician or parent/careers felt that further adjustments to AEDs was not warranted. For more details on patient recruitment and inclusion criteria see chapter 3.5.

7.3.2. Procedure

This was a double blind, randomised, placebo-controlled, cross-over study with lamotrigine. See chapter 3.6 for study protocol (Figure 3.7 and Tab. 3.2) and dosage regime (Tab. 3.1).

7.3.3. Neuropsychological test battery

The following cognitive tests were performed at baseline and the end of both placebo and LTG treatment phase during EEG monitoring. All tests were considered suitable for repeat testing.

- Continuous performance test
- FEPSY Verbal and Non-verbal Recognition Tests
- Delayed recognition test (SMTS-16): words and faces

- FEPSY Computerised Visual Searching Task
- Binary choice reaction time
- N-Grams memory test: words and corsi (also used for TCI testing)

See chapter 3.1 for details about the cognitive test battery.

7.3.4. Statistical analysis

Data were explored by plotting test results at placebo and lamotrigine for each test. As the main purpose of this part of the study was to compare lamotrigine with placebo, the primary analysis was a series of paired t-test for placebo versus lamotrigine across the neuropsychological variables. As 13 variables were examined the level of significance was increased to 0.01. If the correct Bonferroni method (c= k!/2!(k-2)!) were to be used, only a p-value of 0.001 would be considered significant. As we were concerned to detect for a deterioration of cognition, a significance level of 0.01 errs on the side of caution. An ANCOVA with Greenhouse-Geisser test was used to examine period and carry-over effects as well as to examine whether the presence or absence of interictal discharges influenced the result ('reduction of discharges' as between-subject factor). If significant differences between placebo and active treatment were detected an ANCOVA would be used to exclude effects due to multiple comparisons. To inspect the consistency of the findings the data was also analysed by comparing the raw means for all variables using the non-parametric Sign test.

7.4. Results

Of the 64 children screened, 61 patients were included (39 males, 22 females; mean age: 11.5 years, range 7-17 years). All patients underwent randomisation and entered the single-blind baseline phase: 31 were randomised to receive first lamotrigine and then placebo and 30 the reverse order. However, two children were not enrolled in

the treatment phase: one had deterioration in seizure control and the parents of one withdrew consent. Figure 5.1 illustrates the trial profile. The characteristics of both groups were similar (Table 5.1). The seizure frequency did not change significantly during the study (Table 5.2). Forty-seven patients were seizure free at baseline (77%), 40 during the placebo phase (78%) and 39 during the lamotrigine phase (81%). In the three months preceding baseline the mean seizure frequency was 3.43 (SD 13.4, range 0-90) seizures per month, during the placebo phase 3.24 (SD 10.38, range 0-50) seizures per month and during the lamotrigine phase 3.21 (SD 14.69, range 0-90).

Adverse events were evaluated for 59 patients after exclusion of the two patients who were withdrawn in the single blind baseline phase. Apparent treatment related adverse events were observed in 23 of 59 patients (39%) during the lamotrigine phase and in 19 of 52 patients (37%) in the placebo phase (Table 5.3).

Figures 7.1 -7.8 show the box plots comparing placebo with lamotrigine for all tests. For tests measuring scores or correct responses (Tracker test: figure 7.1, FEPSY recognition tests: figure 7.2, SMTS-16 faces and words: figure 7.3, CVST score: figure 7.4, Ngrams compound scores: figure 7.7) a higher value signifies an improvement. For reaction times (CVST reaction time: figure 7.5, Tiger test: figure 7.6, Ngrams corsi and words reaction time; figure 7.8) a higher value signifies a deterioration of cognitive function. None of the tests show an obvious difference between placebo and lamotrigine phase. Some of the tests have extreme values, particularly the tracker test, the SMTS-16 tests, the tiger test and the CVST. Therefore an additional nonparametric analysis is appropriate.

The means for baseline, placebo and lamotrigine (±SD) are given in table 7.1.

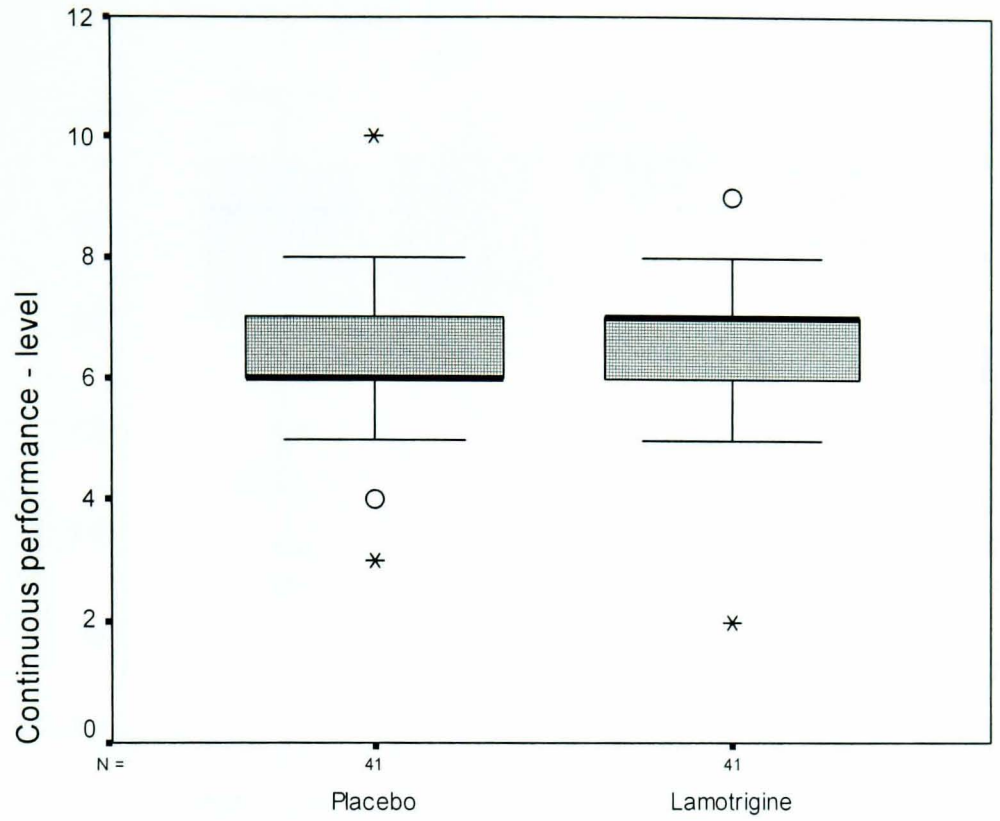


Figure 7.1: Box plot for Tracer test (continuous performance score): no obvious difference between placebo and lamotrigine. o: outliners (cases with values between 1.5 and 3 box lengths from the upper or lower edge of the box), *: extremes (cases with values more than 3 box lengths from the upper or lower edge of the box).

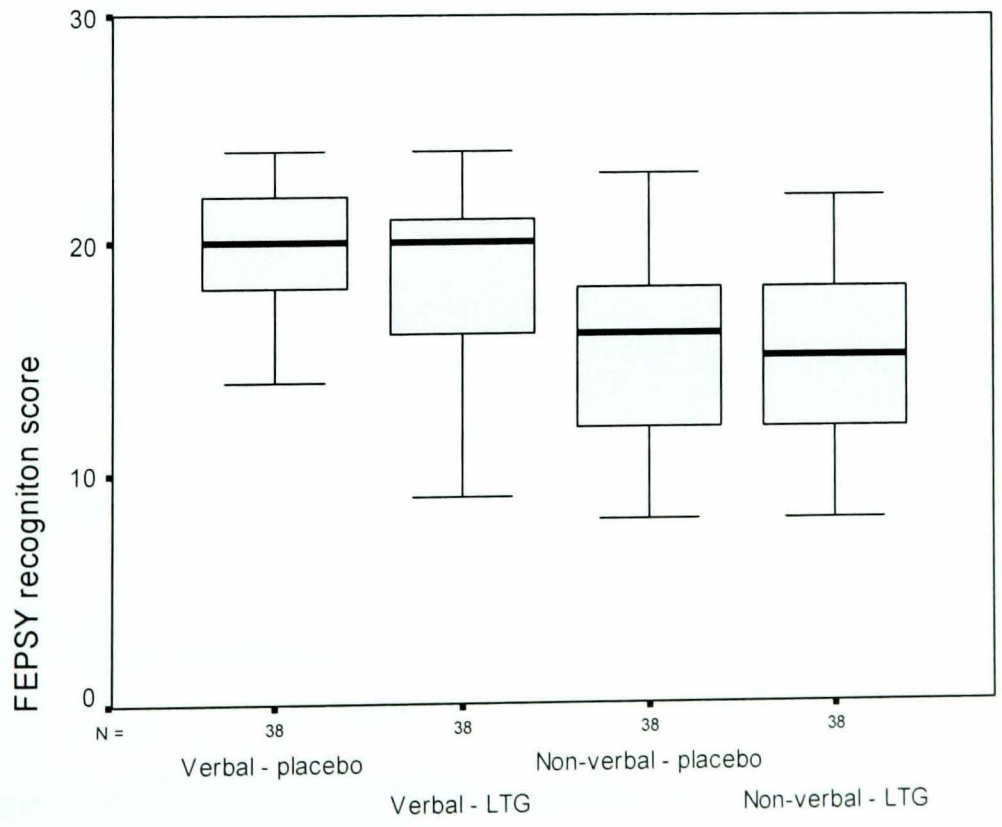


Figure 7.2: Box plot for FEPSY Recognition test: verbal and non-verbal scores. No difference between placebo and lamotrigine. Legend: see figure 7.1

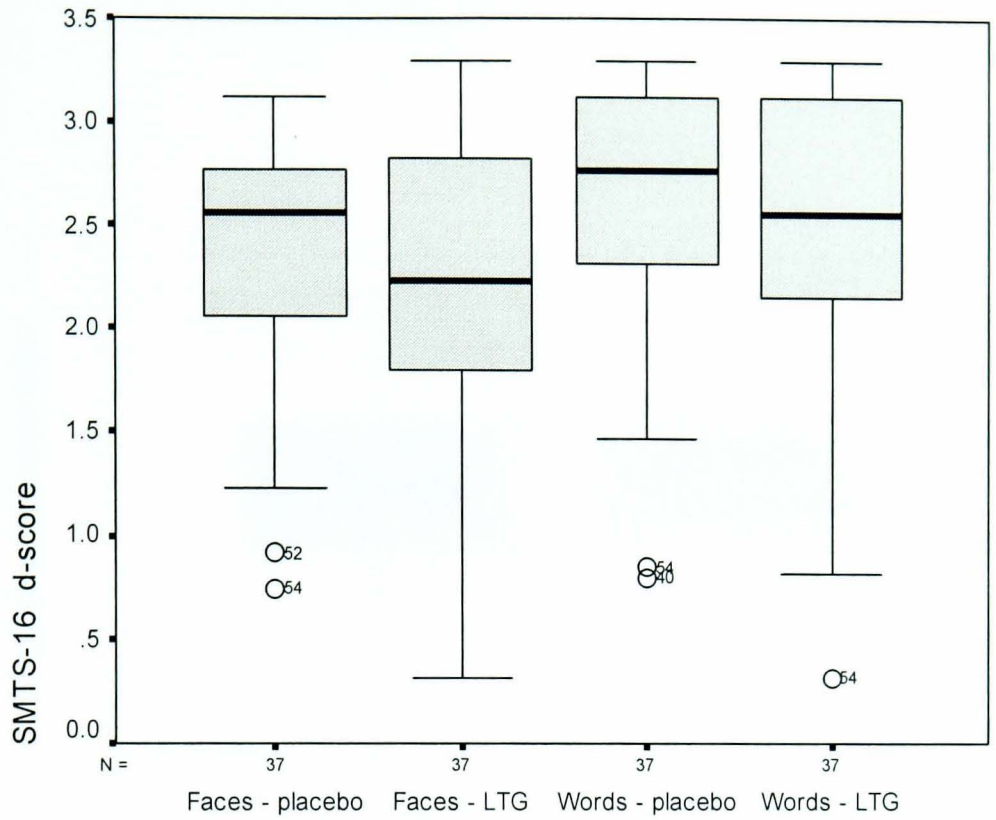


Figure 7.3: Box plot for STMS-16 delayed recognition test: faces and verbal scores. No obvious difference between placebo and lamotrigine. Legend: see Figure 7.1

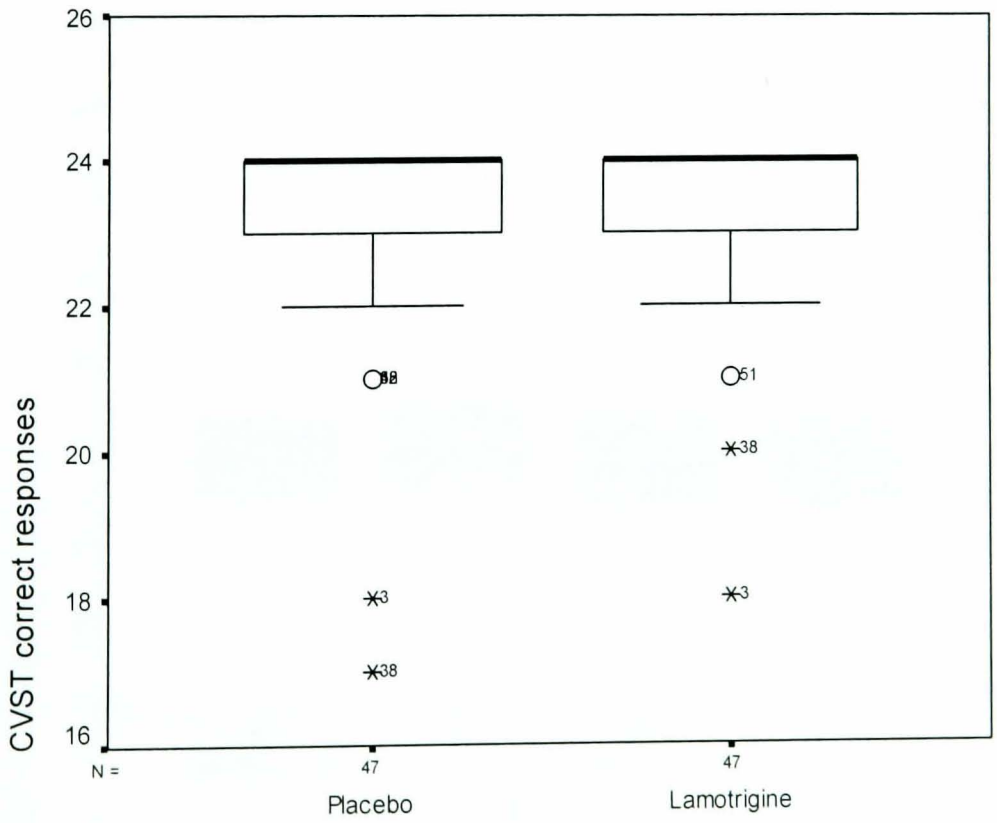


Figure 7.4: Box plot for CVST test (score): no obvious difference between placebo and lamotrigine. Legend: see Figure 7.1

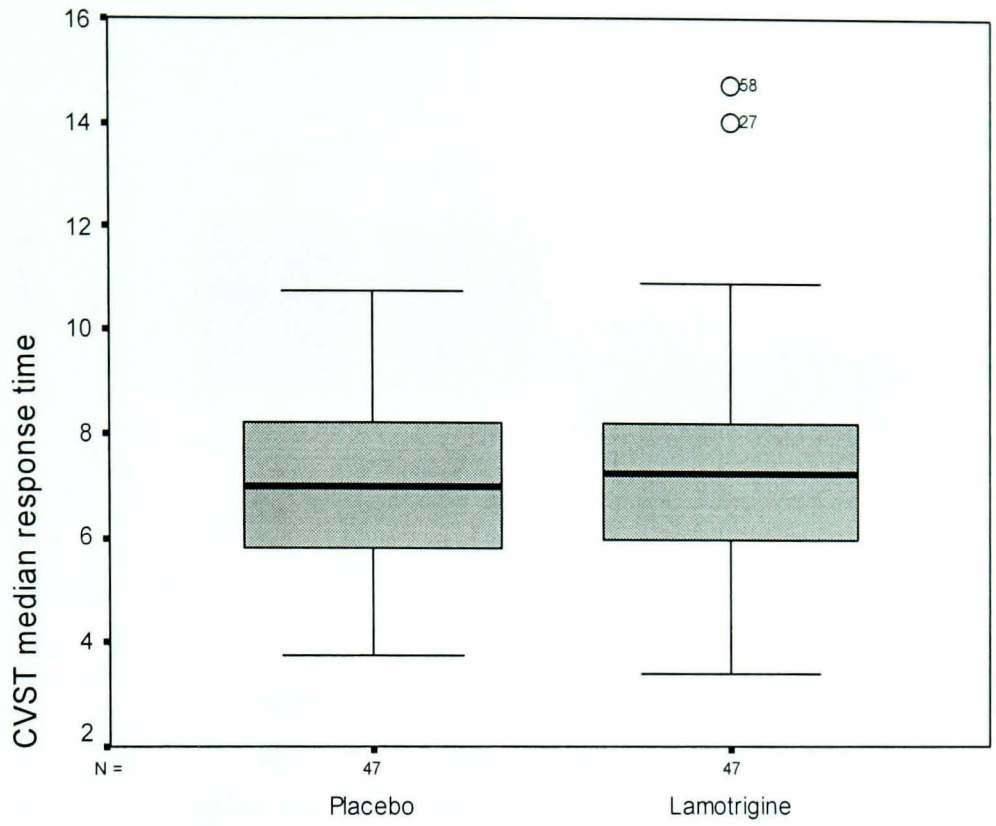


Figure 7.5: Box plot for CVST (median reaction time): no obvious difference between placebo and lamotrigine. Legend: see Figure 7.1

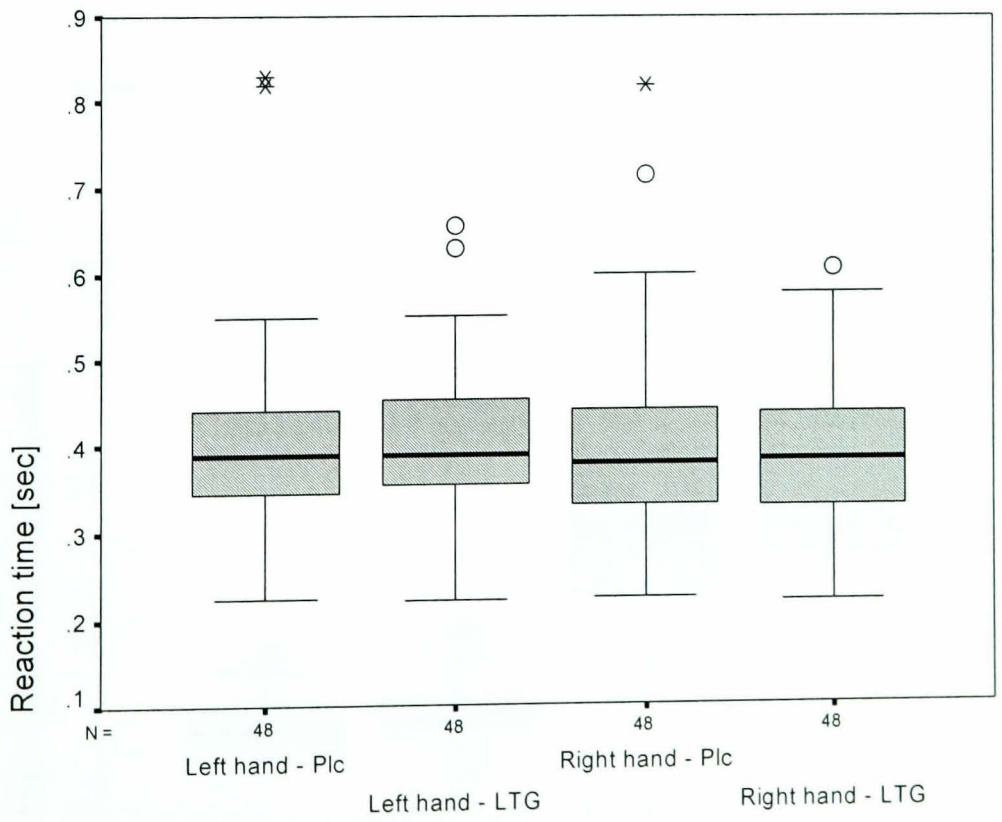


Figure 7.6: Box plot for Tiger test (choice reaction time) no obvious difference between placebo and lamotrigine. Legend: see Figure 7.1

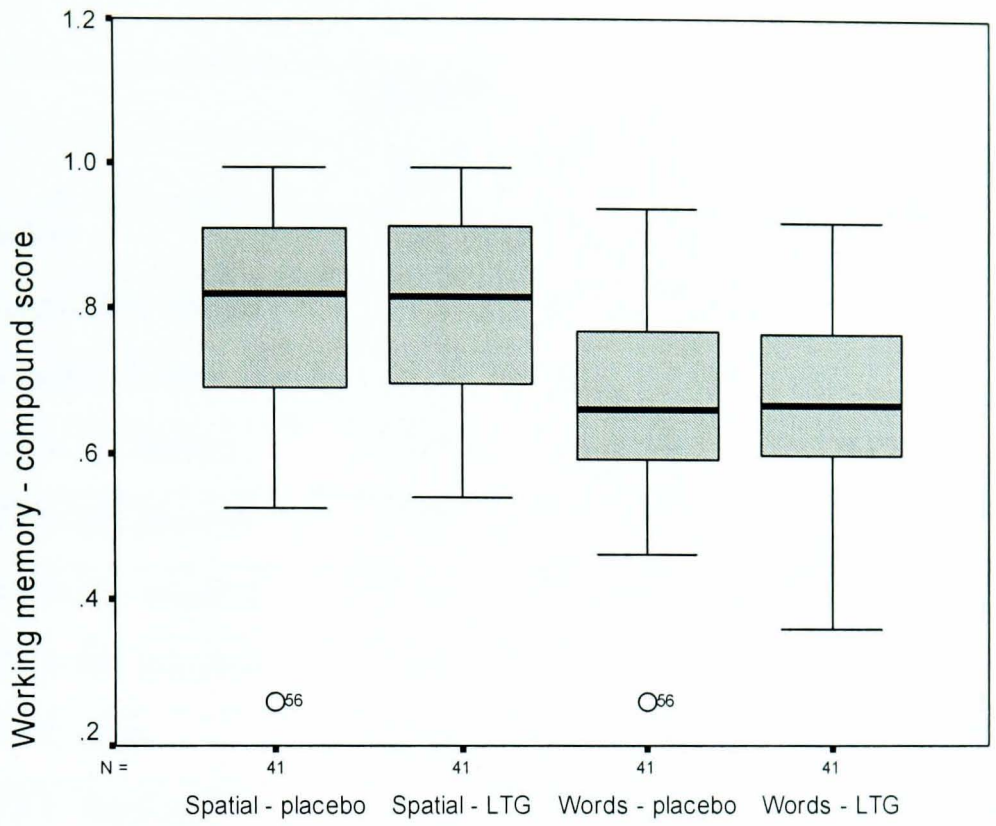


Figure 7.7: Box plot for Ngrams working memory spatial and words (compound score): no obvious difference between placebo and lamotrigine. Legend: see Figure 7.1

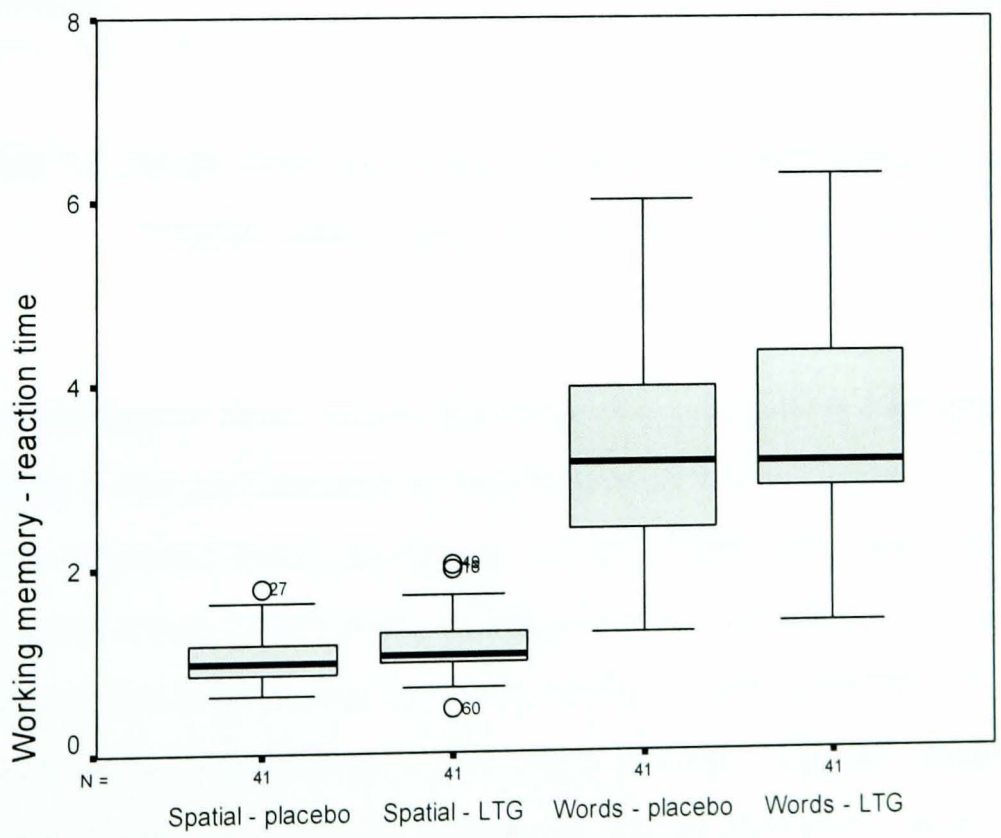


Figure 7.8: Box plot for Ngrams working memory (reaction time): no obvious difference between placebo and lamotrigine. Legend: see Figure 7.1

	Baseline		Placebo		Lamotrigine	
	Mean	±SD	mean	±SD	mean	±SD
Tracker	5.84	1.50	6.43	1.23	6.36	1.14
Recognition verbal	18.20	3.71	19.58	3.35	19.08	3.50
Recognition non-verbal	14.49	3.34	15.05	3.84	15.05	3.52
SMTS-16, faces c	0.08	.25	0.14	.24	0.03	.29
SMTS-16, faces d	2.10	.81	2.41	.60	2.23	.72
SMTS-16, words c	0.12	.28	0.16	.24	0.02	.25
SMTS-16, words d	2.24	.80	2.56	.68	2.43	.78
CVST, corr	22.63	2.10	23.16	1.49	23.43	1.19
CVST, median *	8.16	3.47	6.98	1.94	7.40	2.24
Tiger right *	0.45	.14	0.41	.11	0.41	.09
Tiger left *	0.42	.14	0.39	.11	0.38	.08
Corsi comp	0.73	.16	0.79	.15	0.81	.13
Words comp	0.66	.13	0.67	.14	0.67	.12
Corsi RT *	1.43	.79	1.05	.33	1.13	.34
Words RT *	3.67	1.53	3.37	1.49	3.61	1.08

Table 7.1: Mean scores and reaction times of neuropsychological tests.

* higher score signify a worse result (reaction times).

Comparison of mean values of performance at placebo with lamotrigine revealed slightly better performance on lamotrigine in two variables (CVST score, Ngrams corsi compound score), no change in three (Tiger right hand reaction time, FEPSY recognition non-verbal score, Ngrams words compound score) and slight deterioration of performance in eight (Tracer score, FEPSY recognition verbal score, SMTS 16 faces and words, CVST reaction time, Tiger left hand reaction time, Ngrams corsi reaction time, Ngrams words reaction time). None of these differences were significant at a 0.01 level (Table 7.2).

	Paired t-test			Sign test	
	Mean δ	SD	t-test: p	Z	p value
Tracker score	0.00	1.10	1.00		1.00
Recognition verbal	0.71	2.35	0.07	-1.64	0.10
Recognition non verbal	0.26	3.08	0.60	-0.74	0.46
SMTS-16, d faces	0.17	0.74	0.14	0.00	1.00
SMTS-16, d words	0.15	0.66	0.17	-1.44	0.15
CVST, score	-0.26	1.15	0.14		0.26
CVST, median RT *	-0.34	1.56	0.14	0.00	1.00
Tiger left *	0.01	0.06	0.52	-0.31	0.76
Tiger right *	0.02	0.06	0.06	-1.19	0.23
Corsi comp score	-0.01	0.08	0.34	-.47	0.64
Words comp score	0.00	0.07	0.66	-0.15	0.88
Corsi reaction time *	-0.08	0.25	0.05	-2.14	0.03
Words reaction time *	-0.22	1.19	0.23	-1.83	0.07

Table 7.2: Effect of LTG on cognitive function: mean differences between placebo and lamotrigine with results of paired-t tests and the non-parametric Sign test. No significant p value on a 0.01 level was found. Mean δ: mean difference. *are tests which are a negative value score signifies deterioration and a positive score improvement of performance (reaction times). In all other tests negative values signify improvement and a positive score deterioration.

An ANCOVA with repeated measures was used to examine period and carry-over effects. Test values of first, second and third test session were compared with randomisation as between-subject factor. Table 7.3 gives the mean values of all cognitive variables according to test session and the corresponding ANCOVA F and p values. In ten out of 13 variables each consecutive session produced a better result. Only in two variables (tracker test and non-verbal recognition test) was the second session better than the third and in one (SMTS-16 faces) was the first session better than the second and the third best. Comparison using ANCOVA with repeated measures reveals a significant overall period effect ($F(26.98)=1.64$; $p<0.05$). Four

out of thirteen variables showed a significant Greenhouse-Geisser test ($p<0.05$): Tiger test (right and left hand), CVST score and reaction time. All the significant variables showed the typical learning profile, with each consecutive session improving. However, when randomisation is taken into account, there was no significant difference between sessions ($F(26,98)=1.07$; $p=0.4$).

In the delayed recognition test (SMTS-16) there was no relevant bias during baseline, placebo or lamotrigine in either of the tests (faces and words). The C response bias scores were within a small range around neutral bias (Table 5.4). There was no significant change in bias comparing placebo with lamotrigine.

	Faces		Words	
	Mean	SD	Mean	SD
Baseline	0.8	± 0.25	0.12	± 0.28
Placebo	0.14	± 0.25	0.16	± 0.24
Lamotrigine	0.3	± 0.29	0.2	± 0.25

Table 7.3: Bias in delayed recognition test (SMTS-16). Bias was small at all phases (baseline, placebo and lamotrigine) and did not change significantly during active treatment.

The Sign tests similarly showed that the number of means favouring one condition over the other was not significant in any of the 13 variables (Table 7.2). The means favoured lamotrigine over placebo in 5 variables and favoured placebo over lamotrigine in seven variables (scores were even in one variable). Thus, no condition was superior over the other in any of the variables.

Twenty-one and 23 patients had reduction of number and duration of interictal discharges during lamotrigine compared with placebo (see chapter 5). Table 7.5 lists the mean differences between lamotrigine and placebo according to reduction of discharges or no reduction of discharges during active treatment. There was no significant difference between the two patient groups in respect to cognitive side effects during lamotrigine treatment (number of discharges: $F(26,86)=1.95$; ns; duration of discharges: $F(26,86)=1.81$;ns).

	1st session		2nd session		3rd session		ANCOVA (session)		ANCOVA (session*rando)	
	Mean	SD	mean	SD	mean	SD	F	Sig.	F	Sig.
Tracker score	5.84	1.50	6.47	1.01	6.33	1.34	0.39	0.65	0.39	0.65
Recognition verbal	18.20	3.71	19.27	3.86	19.39	2.92	0.28	0.65	0.55	0.50
Recognition non verbal	14.49	3.34	15.38	3.67	14.71	3.68	0.60	0.51	0.54	0.54
SMTS-16, d faces	0.08	0.25	0.05	0.29	0.12	0.25	2.37	0.11	2.47	0.10
SMTS-16, d words	2.10	0.81	2.26	0.73	2.38	0.59	2.57	0.09	0.53	0.58
CVST, score	22.63	2.10	23.06	1.52	23.53	1.12	5.83	0.01‡	0.84	0.43
CVST, median RT *	8.16	3.47	7.26	2.12	7.11	2.08	5.38	0.01‡	1.29	0.28
Tiger left *	0.45	0.14	0.41	0.11	0.40	0.09	5.05	0.01‡	0.14	0.85
Tiger right *	0.42	0.14	0.39	0.11	0.38	0.08	6.03	0.01‡	0.74	0.46
Corsi comp score	0.73	0.16	0.78	0.15	0.82	0.13	1.00	0.36	1.30	0.28
Words comp score	0.66	0.13	0.67	0.13	0.67	0.13	1.02	0.32	1.07	0.31
Corsi reaction time *	1.43	0.79	1.14	0.35	1.04	0.32	2.36	0.12	1.74	0.19
Words reaction time *	3.67	1.53	3.51	1.12	3.47	1.47	1.96	0.16	0.66	0.47

Table 7.4: Mean values of cognitive variables according to test session. Comparison with ANOVA with repeated measures: Four variables were significant for session (‡Greenhouse-Geisser test: $p<0.05$), but none when randomisation (rando) is taken into account. * higher score signify a worse result (reaction times).

	Reduction of number of ID		No reduction of number of ID		Reduction of duration of ID		No reduction of duration of ID	
	Mean δ	SD	Mean δ	SD	Mean δ	SD	Mean δ	SD
Tracker score	.05	.89	-.05	1.28	.00	.89	.00	1.30
Recognition verbal	.88	2.29	.57	2.44	.89	2.22	.55	2.50
Recognition non verbal	.24	2.31	.29	3.65	.50	2.50	.05	3.58
SMTS-16, d faces	.21	.75	.14	.73	.25	.75	.10	.73
SMTS-16, d words	-.04	.70	.32	.60	-.04	.68	.34	.61
CVST, score	-.05	.83	-.41	1.34	-.05	.79	-.44	1.39
CVST, median RT *	-.32	1.43	-.35	1.68	-.35	1.36	-.33	1.75
Tiger left *	.00	.05	.01	.07	.00	.05	.01	.07
Tiger right *	.01	.04	.02	.07	.01	.04	.02	.07
Corsi comp score	.01	.07	-.03	.08	-.01	.09	-.02	.06
Words comp score	-.01	.06	.00	.08	-.01	.07	.00	.08
Corsi reaction time *	-.11	.26	-.05	.24	-.12	.26	-.04	.24
Words reaction time *	-.07	1.47	-.34	.92	-.26	1.52	-.19	.79

Table 7.5 Mean differences (mean δ) of cognitive tests according to suppression of interictal discharges during active treatment.

7.5. Discussion

This is the first controlled study evaluating cognitive side effects of lamotrigine in children with epilepsy using formal cognitive testing. We found no significant cognitive impairment during active treatment compared with placebo.

Our findings are in concordance with previous reports in healthy volunteers (Cohen et al., 1985; Hamilton et al., 1993; Martin et al., 1999; Meador et al., 2000; Aldenkamp et al., 2002) and adults with epilepsy (Banks et al., 1991 Smith et al., 1993; Brodie et al., 1999; Placidi et al., 2000). Conflicting results have been reported by Ettinger and colleagues (1998): in seven patients with epilepsy and mental retardation, LTG add-on caused both positive and negative psychotropic effects as described by parents and supervising staff. No formal cognitive testing or behavioural scales were used. Due to the double blind, placebo-controlled, cross-over design, patient selection and comprehensive test battery we have avoided several methodological pitfalls described earlier (Devinsky, 1995; Kwan and Brodie, 2001; Brunbech and Sabers, 2002; Loring and Meador, 2004).

We found a significant period effect comparing the three different test sessions with performance improving in each consecutive session. This improvement can be explained by a learning effect but a placebo effect has to be considered also. Even if tests thought to be appropriate for serial testing like a choice reaction time or the CVST we found a clear learning effect. This illustrates the importance of appropriate randomisation and control group as in our study. It also demonstrates the fallibility of studies where the cognitive function of the active drug phase is compared to baseline for example in the study by Placidi et al., (2000). Here the effects of lamotrigine on nocturnal sleep, daytime somnolence and cognitive functions were compared with baseline in 13 adults with drug-resistant focal epilepsy. They did not find a significant difference; however, any deterioration may have been masked by placebo and retest effect. Due to an evenly randomised cross-over design we have avoided this confounding factor.

Several uncontrolled studies have reported improved psychosocial functioning during lamotrigine treatment in patients with epilepsy. This included concentration, school or work performance and behaviour, particular in patients with learning difficulties. In 50 children with intractable epilepsy, 21 showed a reduction in

absence and complex partial seizures with 5 patients becoming seizure-free following addition of lamotrigine (Uvebrant and Beuziene, 1994). The parents of 24 of these children reported an improvement in their children's "mental state," including longer attention span, improved alertness, and emotional stability. Although they found that the improvement was apparently unrelated to seizure control in some patients, this factor was not controlled for. Eight of thirteen autistic children in this study showed reduced symptoms after the addition of LTG therapy. In a double blind, placebo-controlled, parallel study parents and caregivers of 130 children and adolescents with Lennox–Gastaut completed the Epilepsy and Learning Disability Quality of Life (ELDQOL) questionnaire at baseline and after 16 weeks of add-on lamotrigine treatment. Significant improvement was noted in mood and sociability in the lamotrigine group (Jacoby et al., 1996). Eriksson and colleagues performed a combined open-phase and controlled-phase (double blind, placebo-controlled, cross-over) study with lamotrigine in patients with Lennox-Gastaut syndrome (Eriksson et al., 1998 and 2001). Of the 27 patients completing the open phase, 17 had a reduction of seizures, improvement of behaviour or motor skills (responder group) and 10 were classified as 'non-responder' with no improvement during the open phase. Fifteen patients of the responder group completed the controlled phase. Parents and staff members reported improvement in behaviour of all patients during lamotrigine, compared with the placebo phase. This correlated with a reduction of interictal discharges in most patients, where only half of responders had a more than 50% reduction of seizure frequency. However, no formal testing was performed and obviously due to the inclusion criteria for the controlled phase there is selection bias.

Similar positive findings have also been described by others (Betts et al., 1991; Gibbs et al., 1992; Uldall et al., 1993; Fowler et al, 1994; Buchanan, 1995).

Several confounding factors have to be considered in the open studies without formal testing: (1) bias in patient selection (2) placebo effect, (3) reduction of seizure frequency during active treatment, (4) spontaneous fluctuations of seizure variables and EEG abnormalities (5) spontaneous fluctuations of cognition and behaviour in patients with learning difficulties It is well established that a higher seizure frequency is associated with an impairment of cognition and behaviour (Keith et al.,

1955; Dikmen and Metthews, 1977; Farwell et al., 1985; Dodrill, 1986; Singhi et al., 1992). Thus, it is likely that a reduction of seizure frequency may result in improvement of cognitive function and behaviour. Even a small change of seizure frequency may have an impact or changes in seizure severity may have cognitive effects in some patients even if the absolute number of seizures did not change. Overall many of their patients did have a reduction in seizure frequency which must have influenced their results.

Furthermore, it is unclear whether EEG discharges improved in these patients. A drastic improvement in behaviour and cognition has been described in patients with a reduction of discharges even when no change in seizure frequency was observed (Besag 1995).

Most controlled studies in either healthy volunteers or adult patients with epilepsy could not confirm an improvement in cognitive performance using formal and controlled testing. Only Aldenkamp and colleagues (2002) found evidence for a selective effect of cognitive activation. There are however, several methodological shortcomings: 1) A very small dose of LTG was used, not comparable to VPA in the same study or in fact to the doses used to treat epilepsy. 2) Differences were not consistent, some changes being better for placebo than for LTG and others worse for placebo than for LTG. This is particularly inconsistent for visual reaction time where the dominant showed an opposite result to the non-dominant hand. 3) This raises the question as to whether the statistical method used was appropriate. As 12 factors were analysed, at least 3 could be significant on a 0.05 level by chance, but only one out of 12 cognitive test measurements was actually significant. No findings achieved the $p < 0.001$ level of confidence. Moreover, by using a t-test rather than ANCOVA possible confounding factors were not taken into account, such as hand dominance. 4) The number of volunteers in this study with parallel design was small, only 10 per treatment group, which in view of point 3) is particularly relevant. Thus, the findings may have been due to chance and may lack clinical relevance.

We could not confirm such an improvement of cognitive function in any of our variables. Most of our patients were seizure-free and in the remaining patients seizure frequency did not change significantly. This has two implications: (1) seizure frequency was not a confounding factor in contrast to many open studies described

above. (2) Lamotrigine suppresses interictal discharges better in patients with severe or on-going epilepsy (see chapter 5). There is evidence that interictal discharges are associated with cognitive impairment (see chapter 8) and a reduction of discharges may be associated with an improvement in cognition similar to the improvement we described in chapter 6. Thus, the effect of lamotrigine on interictal discharges and consequently cognition may be clinically relevant in patients with more severe epilepsy but not in patients with mild or well-controlled epilepsy.

However, our study had the disadvantage of polytherapy in most patients. It is well recognised that polytherapy is associated with more cognitive problems (Thompson and Trimble, 1982; Trimble 1987; Duncan et al., 1990). Thus, a possible positive effect on cognitive performance may have been counter-balanced by the negative effect of polytherapy.

In contrast, aggressive behaviour has been associated with lamotrigine, particularly in children with learning difficulties (Besag et al., 1995; Beran and Gibson, 1998). In an international, multicenter study 2.5% of children were found to have behavioural side effects. The authors contributed this behaviour least to patients becoming more alert, active, and demanding (Besag et al., 1995). They argued that this may be a necessary stage in the rehabilitation of such patients following an improvement in seizure control. Insomnia has also been reported in a small proportion of patients (Sadler, 1999), but most of these patients were taking a relatively high dose of lamotrigine. In addition, 'being more alert' and 'suffering from insomnia' are changes which relate to the same process.

It has been suggested that the mode of action of lamotrigine is the cause for the lack of cognitive side effects: lamotrigine reduces glutamate release and consequently neuronal activity through inhibition of voltage-gated sodium (Na1) channels in the slow-inactivated state (Xie et al., 1995). Lamotrigine displays a use-dependent profile with the inhibition of Na1 channels being more pronounced in rapidly firing neuron during epileptic discharges, but presumably not affecting neuronal firing under normal conditions. In addition to its effect at the voltage-gated Na1 channel, lamotrigine also inhibits voltage-operated calcium (Ca21) channels (Wang et al., 1996). Activation of both Na1 and Ca21 channels results in rising intracellular calcium levels and an increased cellular metabolic requirement. Increased energy

demands and cellular calcium levels contribute to excitotoxic cell death, a potential component of permanent cognitive dysfunction. The ability to reduce excitability in general, and calcium ion influx in particular, may explain the ability of LTG to reduce cognitive impairment arising from episodes of ischemia. *In vitro* studies have shown that lamotrigine inhibits glutamate release from rat cortex during hypoxia (Leach et al., 1991), whereas *in vivo* studies have illustrated the cerebroprotective effects of lamotrigine in rodent models of focal ischemia (Smith and Meldrum 1995). Mechanisms of cognition and memory are poorly understood at the molecular level. However, longterm potentiation is a form of synaptic plasticity that may form a basic mechanism for memory and learning (Bliss and Collingridge, 1993). It has more recently been reported that at anticonvulsant doses, lamotrigine had no effect on either the induction or the maintenance of long-term potentiation (Xiong and Stringer, 1997; Otsuki et al., 1998). In the gerbil, temporary bilateral occlusion of the common carotid arteries impairs escape from the Morris water maze and subsequent histological examinations reveal severe deterioration of hippocampal neurons. Gerbils treated with LTG are significantly better at escaping from the water maze and have significantly less ischemic cerebral injury (Wiard et al., 1995). Taken together the existing preclinical data suggests that LTG treatment does not result in any cognitive impairment and can protect against excitotoxic and ischemic insults.

The subjective improvement of cognition in quality of life described in open and controlled studies (Smith et al., 1993; Brodie et al., 1995; Schapel and Chadwick 1996) may also be explained an improvement in mood (see chapter 6).

In conclusion, the results of our study suggest that lamotrigine has no significant cognitive side effects in children with mild epilepsy. Further studies are needed in patents with newly diagnosed epilepsy to evaluate a possible positive effect of lamotrigine on cognition.

Chapter 8: Effect of interictal discharges and TCI on cognition

8.1. *Summary*

Objective: There is evidence that interictal discharges are associated with cognitive impairment in patients with epilepsy. It is unclear whether such impairment is due to the discharges (transitory cognitive impairment or TCI) or whether both are a symptom of an underlying brain pathology. The aim of this chapter was to examine relationships between interictal discharges, TCI and cognitive performance.

Method: Children with mild or well-controlled epilepsy were tested between one and three times using a comprehensive cognitive test battery including TCI testing during EEG monitoring. They were grouped according to the occurrence of interictal discharges and results of TCI testing into three groups: (1) no interictal discharges; (2) interictal discharges, but no TCI; (3) interictal discharges and TCI. Cognitive performance was compared between the three groups using one-way ANOVA.

Results: Sixty patients were tested on a total of 158 occasions. Interictal discharges were found in 54% of any cognitive test session, but only in 37% of sessions were the number of discharges sufficient for analysis. Of these TCI was found in 63% on the first session, in 61% in the second and 50% on the third session in a total of 21 patients. Fourteen patients had consistent TCI results in all the sessions: 10 had TCI in all sessions, and 4 had no TCI in any session. There was a significant correlation between the side of discharges and the type of cognitive deficit (spatial or verbal), after correcting for hemisphere dominance. There was a tendency for patients with interictal discharges to have a poorer performance than patients without discharges and for patients with TCI to have worse performance compared to patients without TCI. This difference was significant for 3 variables of working memory.

Conclusion: Results of this study suggest TCI occurs in approximately half of those patients who have sufficient discharges to be tested, even if their epilepsy is well controlled. Interictal discharges are associated with cognitive impairment, particularly affecting working memory, in children with epilepsy. TCI is likely to be one of the causative factors for this.

8.2. *Introduction*

There is convincing evidence that interictal discharges may be associated with cognitive impairment in patients with epilepsy. Subclinical or interictal discharges are defined as epileptiform EEG discharges not accompanied by clinical events using available methods of clinical observation (Aarts et al., 1984). Although this definition is controversial and not accepted by some (Besag, 1995; Aldenkamp and Arends 2004) is used in this study.

Kløve (1956) found an association of left temporal discharges with lower verbal IQ score, while discharges on the right were associated with lower performance abilities. Patients with frequent discharges did more poorly in a performance measure of the Wechsler Adult Intelligence Scale than patients with infrequent discharges (Parsons and Kemp, 1960). These findings were confirmed by Dodrill and Wilkus (1976) in a large study grouping 90 patients according to the presence or absence, average rate (more or less than 1 per min), and topographic distribution of discharges (focal or generalised). They found that performance and full scale IQ were significantly lower in patients with discharges, particularly in the high frequency and generalised discharge groups. However, these studies provide no evidence as to whether discharges are temporally related to intellectual deficits. Moreover, the question as to whether or not there is a causal relationship cannot be evaluated by simple associations (see Figure 8.1).

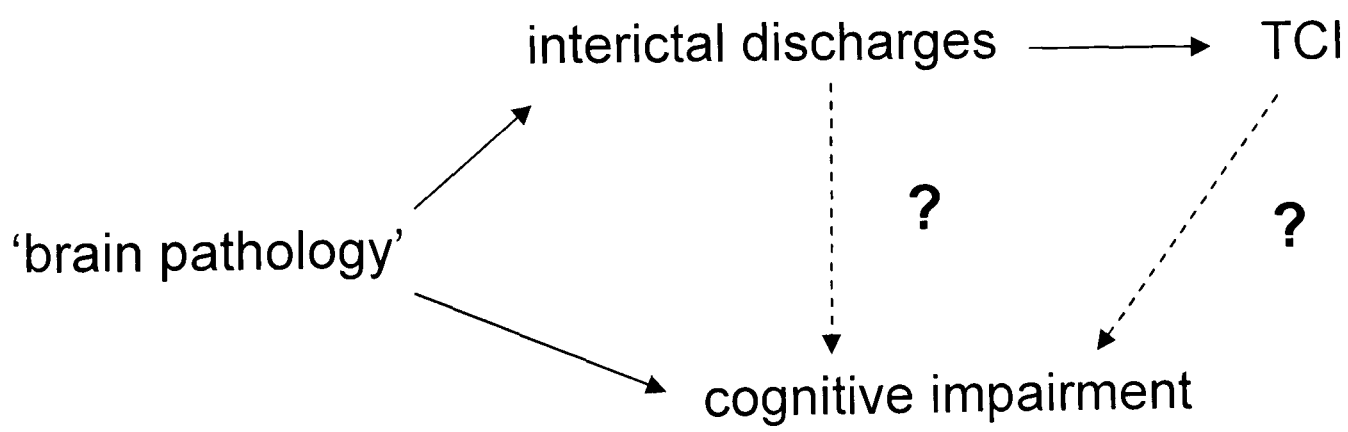


Figure 8.1: Possible interaction between interictal discharges, brain pathology and cognitive impairment.

It has been argued that the EEG abnormalities simply indicate the relative severity and distribution of cerebral pathology or pathophysiology among groups rather than reflecting a specific cause.

In 1939 Schwab developed a method to measure visual reaction times during EEG recording. He found delayed or missing reactions during EEG discharges compared to presentations occurring without discharges. About 50 studies subsequently confirmed a direct temporal association between EEG discharges and brief impairment of cognitive function detectable with appropriate psychological testing (for reviews see Aarts et al., 1984, Binnie, 2003). This was termed TCI (Transitory cognitive impairment); see section 1.4 for more detail.

However, the relation between the duration of discharges and the severity of cognitive impairment, or between the laterality of discharges and the nature of dysfunction has not been fully examined. TCI may impair day-to-day psychosocial function. In children discharges are associated with faster, but less accurate reading (Kasteleijn-Nolst Trenite et al., 1988) and impaired performance in IQ testing with a characteristic subtest profile (Siebelink et al., 1988). In adults driving abilities were significantly impaired during interictal discharges in 3 out of 6 patients with epilepsy and frequent EEG discharges (Kasteleijn-Nolst Trenite et al., 1987).

It remains unclear whether suppression of interictal discharges with antiepileptic drugs (AEDs) can improve cognitive and psychosocial functioning. In a preliminary placebo controlled, add-on study with sodium valproate or clobazam in children with drug-resistant epilepsy, Marston et al., (1993) found improved behaviour associated with reduction of interictal discharges in most patients. Chapter 6 describes the results of our double blind, placebo-controlled, cross-over study with lamotrigine add-on providing evidence that reduction of discharges improves behaviour in children with epilepsy. However, within the same group of patients no improvement of cognitive performance was seen during treatment with lamotrigine (chapter 7).

The aim of this chapter is to examine the relationship between interictal discharges, TCI and cognitive performance in children with well-controlled epilepsy.

8.3. *Methods*

8.3.1. Patients

Patients were recruited from paediatric outpatient clinics at three study sites: Guy's Hospital, King's College Hospital and The National Centre for Young People with Epilepsy (NCYPE, former St Piers Lingfield), UK. Patients aged 7 to 17 years were eligible if they had a confident diagnosis of epilepsy and were seizure free or were having occasional seizures but in whom the responsible clinician or parent/carers felt that further adjustments to AEDs was not warranted. For more details on patient recruitment and inclusion criteria see section 3.5.

Patients were grouped according to the occurrence of interictal discharges and results of TCI testing into three groups: (1) no interictal discharges; (2) interictal discharges, but no TCI; (3) interictal discharges and TCI.

8.3.2. Procedure

This was a double blind, randomised, placebo-controlled, cross-over study with lamotrigine. See section 3.6 for study protocol (Figure 3.7 and Table 3.2) and dosage regime (Table 3.1).

8.3.3. Neuropsychological test battery

Patients were tested on three occasions within a 31 week period. Two were whilst on baseline medication (with or without placebo) and one was after adding lamotrigine to the AED regime. As earlier described lamotrigine did not affect cognitive performance (see chapter 7) and thus all three test sessions were analysed together. On each occasions the following investigations were performed:

- Seizure history
- Ambulatory EEG recording
- Cognitive test battery
- TCI testing

TCI testing was performed using the Ngrams test battery which has been developed from the computerized 'Modified Corsi' test (S.G. Coleshill, PhD 1999). The Ngrams measures working memory, the 'Corsi' subtest spatial memory, and 'words' subtest verbal memory. A Medlec® Profile EEG system by Taugagreining was used for co-registration of EEG signal and for analysis. Sixteen chlorided silver electrodes were placed according to the Modified Maudsley placement at Fp2, Fp1, F4, F3, F8, F7, C4, C3, P4, P3, T4, T3, T6, T5, O2, O1.

The test consists of presenting a sequential string of items on the touch-screen within a 3 x 4 matrix. Recall of the string (item, order of item, location and order of location) was indicated by the subject by touch-selecting items from a menu of 12 possibles, then entering them into the array. Items appeared in a pseudo-randomised sequence. Each subtest consists of 40 trials, 4 of which are practice trials. The sequence length was adaptive to performance: when two consecutive sequences were performed correctly, the length of the sequence was increased by one (minimum length: 3 items, maximum: 5 items). The test was self-paced and depending on the memory capacity and speed of the child each test lasted between 30 and 45 min. It can be used as a working memory test or with real-time EEG co-registration as a TCI test.

For more detail on TCI testing see chapter 3.3.

The following cognitive test battery was used. All tests were thought to be suitable for repeated testing.

- Continuous performance test
- FEPSY Verbal and Non-verbal Recognition Tests
- Delayed recognition test (SMTS-16): words and faces
- FEPSY Computerised Visual Searching Task
- Binary choice reaction time
- N-Grams working memory test: words and corsi (also used for TCI testing)

See chapter 3.1 for details about the cognitive test battery.

8.3.4. Statistical analysis

For Ngrams-words there are four principal fractionated working memory performance scores (Identity: *id*, Order of Identity: *ido*, Location: *loc* and Order of Location: *loco*), together with 2 derivative measures (Match score: *mat* and Compound score: *comp*). For Ngrams-corsi there are only two principal fractionated performance scores (Location: *loc* and Order of Location: *loco*), together with 1 derivative measures (Compound score: *comp*). The Match score for any item in the string is a binary measure of the concordance between the two measures Identity and Location: a match score of one represents the correct item in the correct position; a score of zero represents a mismatch, irrespective of whether the sequence order was correct or incorrect. The Compound score is a general measure of performance including all measured variables. Each record with sufficient number of interictal discharges was analysed to determine whether an association exists between score/reaction time and occurrence of discharges during this particular trial, comparing trials with discharges to trials without discharges in the non-parametric Mann-Whitney test. A sufficient number of interictal discharges was defined as at least four trials with discharges during testing (excluding practice trials) or a maximum of 33 trials with discharges. A patient was considered to have TCI if the p-value was smaller than 0.05 in the compound score or the reaction time. In order to reduce the number of variables and therefore the risk of diagnosing TCI by chance impaired performance in other variables (*loc* or *loco* in Ngrams-corsi; *id, loc, mat, ido, loco* in Ngrams-words) alone was not regarded as TCI.

See chapter 3.3 for more details on TCI analysis.

Correlation between lateralisation and type of cognitive impairment was examined using the chi-square test. Cognitive performance was compared between the three groups using one-way ANOVA. To evaluate subgroups, post-hoc analysis was performed (Scheffe).

8.4. *Results*

Of the 64 children screened, 61 patients were included into the study (39 males, 22 females; mean age: 11.5 years, range 7-17 years). One patient was excluded before cognitive testing was performed (parents withdrew consent). Ten patients were withdrawn before the second testing and another two before the third testing. Six had adverse events, parents of four children withdrew consent and one had protocol violations. Thus, a total of 158 test occasions were performed.

The seizure frequency did not change significantly during the study (Table 5.2). Forty-seven patients were seizure free on baseline (77%), 40 during the placebo phase (78%) and 39 during the lamotrigine phase (81%).

Seven patients were left handed. Six of them had symptomatic partial epilepsy and one had idiopathic generalised epilepsy. Another patient with symptomatic partial epilepsy was ambidextrous. The mean age of onset of left handed patients with symptomatic partial epilepsy was 4.1 years, in contrast to the whole group with a mean age of onset of 6.7 years.

8.4.1. Interictal discharges

On baseline interictal discharges were found in 42 out of 60 (70%) patients during ambulatory recording. In the initial ambulatory EEG recording 19 (31%) children had no discharges and 42 (69%) had discharges during the eyes open phase. In children with discharges the median number of discharges was 3.85/hr (range 0.6 to 115.6/hr, SD 24.68) and the median duration of discharges was 4.75 sec/hr (range 1.0 to 140.8 sec/hr, SD 33.78) (see chapter 5). These discharges were generalised in 11 patients, focal in 17 (right sided in seven, left sided in three and bilateral in seven) and both focal and generalised in 14 patients (with focal discharges right sided in seven, left sided in three and bilateral in four). However, we found interictal discharges only in 33/60, 28/50 and 25/48 patients during cognitive testing on baseline, placebo and lamotrigine respectively. The number of discharges was sufficient for TCI analysis in 34-40% patients. This was due to too few discharges in 7 patients and too many discharges in 2 patients on baseline, too few discharges in 8 patients and too many discharges in 3 patients on placebo and too few discharges in

patients on lamotrigine. The four patients with too frequent discharges had idiopathic partial epilepsy. Table 8.1 summarises the occurrence of interictal discharges for all three test sessions. It becomes clear that lamotrigine does not suppress numbers of discharges in our group of patients (see chapter 5). The percentage of patients with sufficient numbers of discharges for TCI testing was 37% in our population.

	Baseline	Placebo	Lamotrigine	All sessions
Patient sessions	60	50	48	158
ID in ambulatory recording	42 (70)	36 (72)	32 (67)	110 (70)
ID in TCI test	33 (54)	28 (56)	25 (52)	86 (54)
Sufficient ID for TCI analysis	24 (40)	17 (34)	18 (38)	59 (37)

Table 8.1: Occurrence of interictal discharges during ambulatory recording and cognitive testing (in %). id: interictal discharges,

8.4.2. TCI analysis

TCI defined as significantly poorer performance in RT and/or compound score during trials with discharges compared to trials without discharges was found in 21 patients. Nine had TCI only in one test, seven in two tests, three in three tests, one in four, and one in five tests. Thus, 41 test sessions revealed TCI. Table 8.2 list the results of Ngrams Corsi and Ngrams Words on three test occasions.

Ngrams-corsi revealed TCI on baseline in 7 out of 17 patients with sufficient numbers of discharges. In 2 this was due to a significant compound score and in 5 due to a significant reaction time. In a further two patients *loc* was significant and in another *loco*. Interestingly all three patients had TCI at other occasions: one had a significant reaction time, another one had TCI in Ngrams-words on baseline and the last had TCI on placebo in words. On placebo TCI was due to a significant compound score in 4 patients and due to a significant reaction time in one patient. In no other patients was only *loc* or *loco* significant. On lamotrigine TCI was due to a significant compound score in 5 patients and due to a significant reaction time in 1 patient. In no other patients was only *loc* or *loco* significant.

	No ID	Insuf. ID	p<0.05	ns	Too many
BL (n=60)					
loc			4 (7)	13 (21)	
loco			3 (5)	14 (23)	
comp			2 (3)	15 (25)	
RT			5 (8)	12 (20)	
Comp/RT	32 (53)	9 (15)	7 (11)	10 (17)	2 (3)
PLC (n=49)					
loc			3 (6)	13 (26)	
loco			4 (8)	12 (24)	
comp			4 (8)	12 (24)	
RT			1(2)	14 (29)*	
Comp/RT	24 (49)	8 (16)	5 (10)	10 (20)	2 (4)
LTG (n=48)					
loc			4 (8)	10 (21)	
loco			5 (10)	9 (19)	
comp			5 (10)	9 (19)	
RT			1 (2)	13 (27)	
Comp/RT	25 (52)	8 (17)	6 (13)	8 (17)	1 (2)

Table 8.2 (a): TCI in Ngrams Corsi test. Number of patients with significantly impaired performance during interictal discharges (% of patients). Only a significant difference in RT or Comp is considered as TCI, Impaired function in other variables is not regarded as TCI. ID: interictal discharges, insuf: insufficient, BL@ baseline, PLC: placebo, LTG: lamotrigine, loc: location, loco: order of location, comp: compound score, RT: reaction time, comp/RT: in reaction time or compound score. * one RT measurement failed.

	No ID	Insuff ID	TCI	No TCI	Too many
BL (n=58)					
Id			6 (10)	15 (25)	
Loc			6 (10)	15 (25)	
Mat			4 (7)	17 (28)	
ido			4 (7)	17 (28)	
Loco			5 (8)	16 (27)	
Comp			8 (13)	13 (22)	
RT			7 (12)	14 (25)	
Comp/RT	29 (50)	6 (10)	10 (17)	11 (19)	2 (3)
PLC (n=49)					
Id			2 (4)	14 (29)	
Loc			1 (2)	15 (31)	
Mat			3 (6)	13 (27)	
ido			2 (4)	14 (29)	
Loco			2 (4)	14 (29)	
Comp			3 (6)	13 (27)	
RT			3 (6)	13 (27)	
Comp/RT	24 (49)	7 (14)	6 (12)	10 (20)	2 (4)
LTG (n=48)					
Id			6 (13)	9 (19)	
Loc			0 (0)	15 (31)	
Mat			2 (4)	13 (27)	
ido			4 (8)	11 (23)	
Loco			1 (2)	14 (29)	
Comp			6 (13)	9 (19)	
RT			5 (10)	10 (21)	
Comp/RT	24 (50)	8 (17)	7 (15)	8 (17)	1 (2)

Table 8.2 (b): TCI in Ngrams Words test: Number of patients with significantly impaired performance during ID (% of patients). Legend see (a). id: identity, mat: matching, ido: order of identity.

Ngrams-words revealed TCI on baseline in 10 out of 21 patients with sufficient numbers of discharges. In 3 this was due to a significant compound score, in 2 due to a significant reaction time and in 5 due to both compound score and reaction time being significant. In a further four patients *loc* was significant. Again, all four patients had TCI on other occasions; one had a significant reaction time, another two had TCI in Ngrams-corsi on baseline and the last had TCI on lamotrigine in Ngrams-corsi. On placebo TCI was due to a significant compound score in 3 patients and due to a significant reaction time in 3 patients. In a further patient only *id* was significant, in one *loc* and *loco*, in one *mat* and in another only *loco*. All but one of these four patients had TCI on other occasions: two for reaction time and one for Ngrams-words at baseline and for Ngrams-words on lamotrigine. On lamotrigine TCI was due to a significant compound score in 2 patients, due to a significant reaction time in 1 patient and in 4 due to both compound score and reaction time being significant. In a further patient only *id* was significant, and in another one *id* and *ido*. One of them had TCI for reaction time, the other had no TCI on any occasion. Tabe 8.3 summarises TCI results.

Note that included in this table are also patients without interictal discharges or insufficient number of discharges for statistical analysis. Numbers differ from Table 8.1 because in Table 8.2 results are listed separately for Ngrams-corsi and words. If only patients with sufficient discharges are considered we found TCI in 33 to 41% of patients in the Ngrams-corsi and in 38-48% in Ngrams-words (see Table 8.3).

TCI @	Spatial	Verbal	Either
Baseline n=24	41%	48%	63%
Placebo n=18	33%	38%	61%
Lamotrigine n=18	36%	47%	55%
Any phase n=30	48%	52%	70%

Table 8.3: Summary of TCI results at different test sessions in patients with sufficient numbers of discharges during testing.

Eight out of 26 patients with symptomatic partial epilepsy had sufficient interictal discharges at some point during the study and 6 of those had TCI. Seven out of 18 patients with idiopathic generalised epilepsy had sufficient interictal discharges and 4 of those had TCI. Fifteen out of 16 patients with idiopathic partial epilepsy had sufficient interictal discharges and 11 of those had TCI. These included 2 patients with atypical partial epilepsy, 7 patients with benign epilepsy with centro-temporal spikes (BECT) and 2 patients with childhood epilepsy with occipital paroxysms. There was a tendency for patients with seizures (n=20) to be more likely to have TCI (9 out of 10 with sufficient discharges) than patients without seizures (n=40) (8 out of 20 with sufficient discharges) but this difference was not significant (χ^2=2.857; df=1; p=0.091).

Twenty patients had repeated TCI testing. Ten patients had two separate sessions three months apart and ten patients had 3 sessions with 3 months in between each session. This was distributed as follows:

- TCI/TCI/TCI 4 patients
- TCI/TCI 6 patients
- no TCI/no TCI/no TCI 2 patients
- no TCI/no TCI 2 patients
- TCI/TCI/no TCI 2 patients
- TCI/no TCI/no TCI 2 patients
- TCI/no TCI 2 patients

Thus, 14 patients had consistent results in all the sessions they did: 10 had TCI in all sessions, and 4 had no TCI in any session. Six patients had mixed results, but only two had TCI on baseline and/or placebo but not on lamotrigine.

Table 8.4 summarises the association between lateralisation of discharges with the type of test in which TCI was found. Twenty one patients performed 41 positive TCI tests, four had TCI for both Corsi and Words. Although there was a tendency for left sided discharges to cause TCI in Words, this was not the case for right sided discharges (χ^2=5.909; df=4; ns).

TCI in / ID	Corsi	Words	Both	Total
Right sided	5	9*	1	15
Symmetrical	8	5		16
Left sided	1	5	3	6
Total	14	19	4	37

* 5 were left handed,

Table 8.4: Association between TCI and lateralisation of epileptiform activity

However, of the nine positive Ngrams-words tests during right-sided discharges five were from left-sided patients (five positive test sessions of three patients). After correction for hemisphere dominance the chi-square test reaches a significant level (χ^2=9.840; df=4; $p<0.05$).

Three left handed patients with right-sided discharges had TCI in the Corsi test; no left handed patient with left-sided discharges had TCI in the Corsi test. Thus, we found a significant correlation of side of discharges to the type of test (spatial or verbal), when correcting for dominant hemisphere in words. Table 8.4 also demonstrates that we found that TCI was just as common during focal interictal discharges as during bilateral or generalised EEG discharges.

8.4.3. Relationship of ID, TCI and cognitive performance

To evaluate whether interictal discharges or TCI effect overall cognitive performance, patients were grouped into the following groups: (1) no interictal discharges (n=94), (2) interictal discharges, but no TCI (n=24), (3) interictal discharges causing TCI (n=36). Patients with insufficient discharges for TCI analysis were grouped in the not discharge group. Trials with too many discharges for analysis were not included in the analysis, because the number of trials was too small (n=3) to constitute a separate group, but inclusion in any other group did not appear logical. Table 8.5 summarises comparison of test performance between groups for 13 cognitive test variables at 158 test occasions.

	No ID		ID, no TCI		ID & TCI		ANOVA	
	mean	SD	mean	SD	Mean	SD	F	Sig.
Tracker level	6.33	1.38	6.33	0.86	5.75	1.44	2.50	ns
Recognition v	18.97	3.65	20.18	2.46	18.10	3.84	1.86	ns
Recognition nv	14.82	3.59	15.29	3.04	14.50	3.89	0.27	ns
SMTS-16, faces	2.25	0.74	2.37	0.67	2.09	0.75	0.93	ns
SMTS-16, words	2.46	0.76	2.45	0.69	2.20	0.83	1.26	ns
CVST score	23.10	1.72	23.30	0.93	22.68	2.07	1.08	ns
CVST, RT*	7.27	3.01	7.94	1.64	8.09	2.49	1.39	ns
Tiger RT, left*	0.42	0.13	0.43	0.07	0.44	0.11	0.32	ns
Tiger RT, right*	0.40	0.13	0.41	0.08	0.41	0.11	0.35	ns
corsi comp score	0.81	0.16	0.75	0.12	0.72	0.14	4.79	0.01
corsi RT*	1.15	0.60	1.19	0.35	1.31	0.53	1.06	ns
words comp	0.70	0.13	0.62	0.11	0.63	0.11	4.98	0.008
words RT*	3.22	0.97	3.66	0.83	3.87	1.68	3.65	0.029

Table 8.5: Mean values of cognitive test according to the three groups, as well as results of One-way ANOVA. * are variables where higher values indicate worse performance (reaction times).

There was a tendency for patients with interictal discharges to have a poorer performance than patients without interictal discharges and for patients with TCI to have a poorer performance than patients without TCI (with or without interictal discharges).

Performance was worst in patients with discharges for 12 out of 13 variables compared to patients without interictal discharges and in patients with TCI for 10 out of 13 variables compared to patients without TCI (Tab. 8.5). This difference was significant for 3 out of 4 working memory tasks: spatial Ngrams compound scores and verbal Ngrams compound scores and reaction time ($p< 0.05$).

Figure 8.1 a and b show the mean compound scores and reaction times for the three groups in the working memory tests. Post-Hoc analysis (Scheffe) revealed significant differences between `no ID` and `TCI` group in all three tests ($p<0.05$).

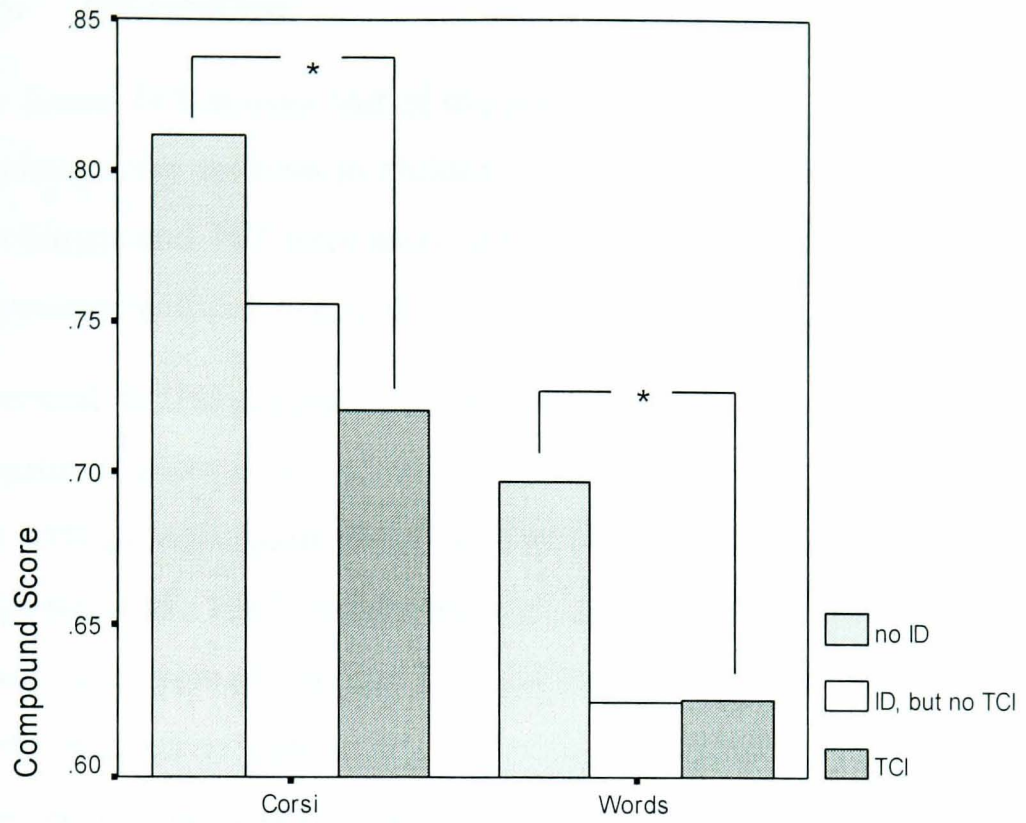


Figure 8.2 (a): Mean compound scores in Working memory test (Corsi: spatial; Words: verbal) according to presence or absence of ID and TCI. Higher values mean better performance. * $p<0.05$ in post-Hoc analysis.

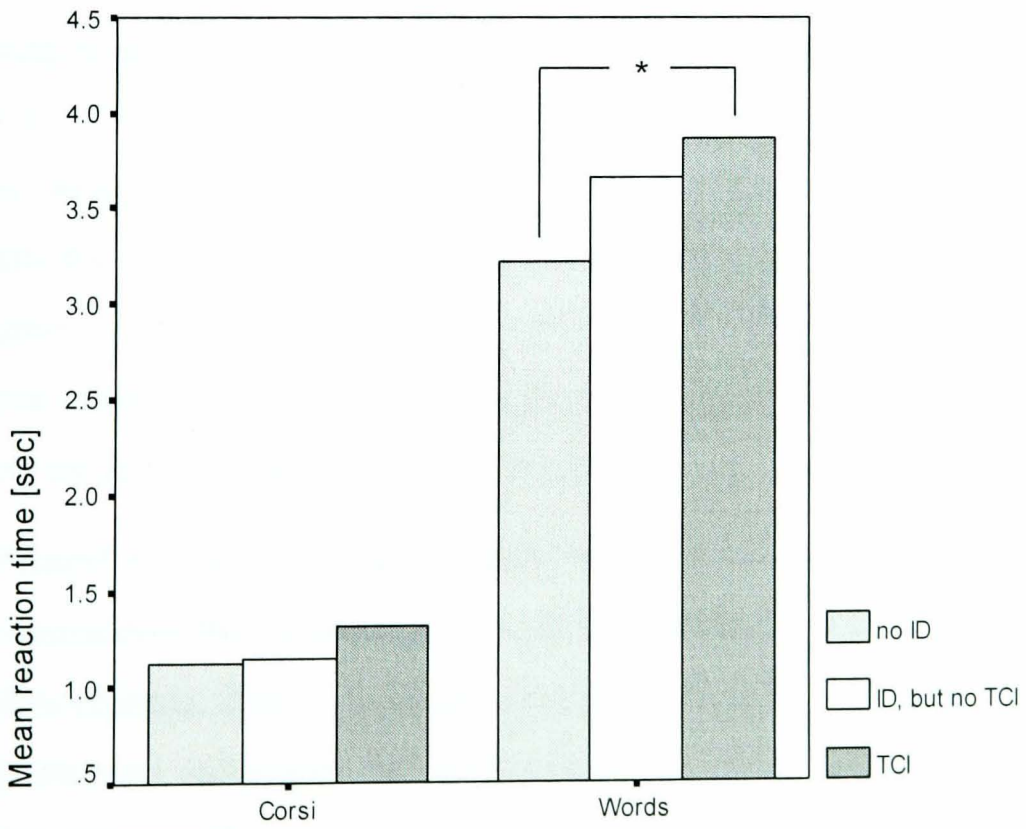


Figure 8.2 (b): Mean reaction times in Working memory test (Corsi: spatial; Words: verbal) according to presence or absence of ID and TCI. Higher values mean worse performance. * $p<0.05$ in post-Hoc analysis.

8.5. *Discussion*

We found TCI in over half of the patients with sufficient numbers of interictal discharges for analysis in children with well-controlled or mild epilepsy. Interictal discharges and TCI were associated with worse overall working memory compared to patients without interictal discharges.

Interictal discharges are common phenomena in patients with epilepsy. Around 50% of patients show interictal discharges during a routine 30 min waking EEG recording, but 85% of individuals do so on some occasions (Ajmone Marsan and Zivin, 1970; Salinsky et al., 1987, Sundaram et al., 1990). Interictal discharges are also found in family members of children with epilepsy (Gerken and Doose, 1973), and even in 1 - 3.5% of children without a history of clinical seizures (Eeg-Olafson et al., 1971; Cavazzuti et al., 1980). EEG discharges in general occur most readily in a relaxed, eyes-closed state and are suppressed by psychological testing.

Detection of TCI demands a high initial discharge rate or a test that participants tolerate long enough to capture sufficient discharges and does not suppress discharges (Binnie, 2003). Although 70% of our patients had discharges in the ambulatory EEG recording, only just over a third had sufficient discharges during testing to perform TCI analysis. Similar findings have been described by Kooi and Hovey (1957), Tizard und Margerison (1963a) and Rugland (1990). Nevertheless, considering the discharge rate of most patients was not very high, the Ngrams test fulfils the criteria for a routine test for TCI according to Aarts et al. (1984) not to suppress discharges so that testing is impossible. In some patients with idiopathic partial epilepsy discharge rate was even too high to allow statistical analysis, as there were too few discharge-free trials for comparison.

We found TCI in 35% of all patients, but if only patients with sufficient discharges are considered the percentage (50 – 60% per test session) is similar to that in other studies (Binnie, 2003). As some patients were tested up to three times the number of positive tests was higher than so far described. This is most likely because we used both a compound score and reaction time. The 'Modified Corsi' test introduced by Binnie and co-workers (Aarts et al., 1984; Binnie et al., 1987) has to be considered as the 'gold standard' in TCI testing. They compared the number of correctly performed trials rather than a compound score and did not include the reaction time. Other

studies measured only the reaction time (Shimanzono et al., 1953; Tizard and Margerison, 1963a; Davidoff and Johnson, 1964; Mirsky and Van Buren, 1965. Hutt and Fairweather, 1975; Pressler, 1997). Simple reaction time tests are not sensitive to TCI, particularly in focal discharges (Sellden, 1971), whereas more complex reaction time tasks detect TCI in similar numbers to complex memory tests (Hutt and Fairweather, 1975; Pressler, 1997). One could argue that by including more variables we only increased the statistical probability to find a positive result rather than increasing the sensitivity of the test. However, even if one included all sub-variables of the compound score only one further patient would test positive for TCI. This was a patient with very frequent discharges, who had been excluded from analysis because of too frequent discharges at 3 out of 6 test sessions. If increased probability was random one would expect more patients to test positive (10% per variable).

It is known that focal discharges have a specific effect on test performance (Aarts et al., 1984; Shewmon and Erwin, 1988a). See section 1.4.3.3 for more details. We could for the first time confirm the effect on a larger group of patients after correction for hemisphere dominance. It is interesting to note that most of our left handed patients had symptomatic partial epilepsy (six out of seven patients) with the presumed lesion in the left hemisphere. These children have a younger age of onset than the whole group. Three of the left sided patients had impaired verbal memory during right sided discharges. This correlates with the expected 50% of left handed subjects with right sided language dominance. Shewmon and Erwin (1988 a and b) showed lateralised effects of focal discharges on reaction times when the stimulus was presented in the visual field contralateral to the discharge or when the response was made with the contralateral hand. Thus, TCI is a specific impairment of cognitive function of the brain region involved in interictal discharges and not a global impairment of attention or channel capacity (Tizard und Margerison, 1963; Hutt et al., 1977). Some patients will have impairment of reaction time, while others will have an impairment of verbal or spatial memory. Consequently, using a test with both modules will increase the sensitivity of the test. Nevertheless, it is important to reduce the risk of false positive test results, and the compound score rather than two (Ngrams-corsi) or four variables (Ngrams-words) appears a good compromise.

The test-retest stability of Ngrams was relatively good: 14 patients had consistent results on retesting, whereas 6 patients had inconsistent results. This is definitely more than expected by chance. Considering the fluctuant nature of interictal discharges (see chapter 5), it is not surprising that TCI will not be found on every test occasion. Detection of TCI depends on discharge frequency. Too few or too many make statistical analysis impossible. More discharges increase the probability of disturbance. Furthermore, discharges occurring during stimulus presentation (Mirsky and Van Buren, 1965) or within the preceding 2 seconds (Binnie et al., 1987 have a greater effect than discharges occurring during the response phase. A discharge during serial presentation is most likely to impair recall of the last item (Hutt and Gilbert, 1980). This suggests a disturbance of sensory or perceptual mechanisms or reduced capacity of working memory. Thus, failure to detect TCI does not indicate its absence: the number of discharges may be insufficient or not at the appropriate time of the trial. In other patients, the nature of the test may be inappropriate.

This illustrates the predicament of TCI testing: In everyday life impairment from interictal discharges in children may be more common than indicated by formal testing. In most situations children are presented with new stimuli and often they are required to cope with both presentation of stimuli and respond at the same time. On the other hand children may be able to compensate for the impairment due to EEG discharges in ways poorly understood as these situations are difficult to simulate in the EEG lab. There is evidence that least scholastic performance is impaired in children with epilepsy and interictal discharges (Siebelink et al., 1988). Chapter 6 illustrated that suppression of EEG discharges can improve behaviour.

We found evidence that children with well-controlled epilepsy and interictal discharges have the same percentage and characteristics of TCI than patients with on-going epilepsy. In addition we found TCI in patients with idiopathic or benign partial epilepsy. This is a particularly interesting group of patients with regard to TCI because according to the definition by the international classification of epileptic syndromes these syndromes are age-dependent, idiopathic, non-lesional and not accompanied by neurological deficits. The most common syndrome is that of BECT. Theses children have frequent interictal discharges, yet seizures are infrequent and easily controlled, if AED treatment is required at all. This has implications for

treatment strategies in patients with epilepsy. Only two studies have described TCI in benign partial epilepsy (Binnie et al., 1992; Pressler, 1997). See section 1.4.6. for more details. We were able to confirm these findings detecting TCI in 11 out of 15 patients with idiopathic partial epilepsy, including children with BECT, childhood epilepsy with occipital paroxysms and atypical benign partial epilepsy. Some of the behavioural and cognitive problems described in these syndromes may be caused by TCI. Notwithstanding, prolonged nocturnal spike-wave activity is related to cognitive dysfunction in some patients with idiopathic partial epilepsy as has been described in children with Landau-Kleffner syndrome (Robinson et al., 2001) or ESES (Jayakar et al., 1991).

We were able to show a relationship between interictal discharges, TCI and overall cognitive performance. Although it has been suggested in the past that patients with frequent interictal discharges have impaired cognitive performance (Kløve, 1956; Parsons and Kemp, 1960; Dodrill and Wilkus, 1976), for the first time patients with interictal discharges were divided into patients with and without TCI. Our study confirms these findings, but furthermore suggests that TCI plays a causative role in the cognitive impairment associated with interictal discharges, because in the same patients a temporal relationship was proven during the TCI test. It goes without saying that other factors also play a role in the neuropsychological impairment of people with epilepsy.

Clearly TCI analysis differs from group analysis although both show a significant impairment in working memory. TCI testing is an intra-individual analysis of performance comparing performance with and without discharges within the same subtest. In contrast the group comparison is an inter-individual analysis comparing groups of patients according to the presence or absence of interictal discharges and TCI. It is reassuring that patients with TCI in a working memory test have overall worse performance of working memory compared to other patients. This confirms that TCI is a realistic impairment rather than a random statistical flaw. It also makes clear that a wide range of tests is necessary to be able to detect impairment in different individuals. Further studies are needed including a wider test battery. Only then would it be possible to evaluate a possible effect of medication on overall cognitive performance.

Chapter 9: Discussion

9.1. Summary of main findings

The main theme of this thesis addresses the question as to whether interictal discharges have a direct effect on cognition and behaviour in children with epilepsy and whether suppression of discharges improves psychosocial function.

The main findings of this thesis were:

- Interictal discharges are common in children with epilepsy even if seizures are well controlled. Gender and type of epilepsy may influence the frequency of interictal discharges.
- The spontaneous fluctuations of discharges in ambulatory recordings were considerable; number and duration varied more within than between subjects. Lamotrigine reduced the duration of discharges per hour, but not the total number per hour.
- During active treatment with lamotrigine global rating of behavior significantly improved only in patients who showed a reduction in either frequency or duration of discharges, but not in patients without a change in discharge rate. This improvement was mainly seen in patients with partial epilepsy.
- Lamotrigine had no significant effect on cognitive performance in children with epilepsy, specifically not on continuous performance, binary choice reaction time, verbal and non-verbal recognition, a computerised visual searching task, verbal and spatial delayed recognition and verbal and non-verbal working memory. Results were not influenced by the reduction of interictal discharges during active treatment.
- TCI was found in over 50% of patients with sufficient discharges for analysis. There was a significant correlation of side of discharges to the type of deficit (spatial or verbal), after correction for hemispheric dominance. Interictal discharges were associated with impaired memory performance, particularly in patients testing positive for TCI.

9.2. Considerations

There are other circumstances during which interictal discharges have a negative impact on cognition and behaviour which are distinct from TCI. The most important are: Nocturnal EEG discharges in children with ESES or Landau-Kleffner syndrome, autistic regression and non-convulsive status epilepticus.

In the syndrome of ESES (see chapter 1.1.3.6) it is generally accepted that the severe cognitive deficits in the course of the syndrome are due to the frequent nocturnal epileptiform EEG discharges (Patry et al., 1971; Tassinari et al., 1985). There also is a relationship between the disappearance of these EEG abnormalities and improvement of function, although this is still under debate (Robinson et al., 2001). Nonetheless there is consensus that in ESES there is no definite evidence to what extent the discharges itself, the disturbed sleep, or the various underlying aetiologies cause the cognitive deterioration.

Landau-Kleffner syndrome (see chapter 1) is often seen as the paradigm syndrome to demonstrate the relationship between epileptiform EEG discharges and cognitive impairment. The EEG shows nocturnal epileptiform discharges, very similar to ESES, and sometimes centro-temporal spikes. Some argue that Landau-Kleffner syndrome is secondary to an active epileptic focus in the areas supporting language and point to the intermittent character of the language symptoms (Deonna, 1995). Others consider the epileptiform EEG discharges an epiphenomenon reflecting underlying brain pathology, rather than the direct cause of the language disorders (Holmes et al., 1981).

Autistic regression may also give some evidence on the effect of epileptiform EEG discharges. Some children with autism regress from a normal or mildly delayed baseline. Those children have a worse prognosis with respect to IQ and core features of autism. Tuchman and Rapin (1997) found no significant difference in the prevalence of interictal discharges with or without epilepsy between the group of children with a history of regression and those without. However, if children with epilepsy were excluded from the analysis, there was a significant increase in interictal discharges in those with a history of regression (19% vs. 10% - $p<0.05$). Tuchman has called this "autistic epileptiform regression" (Tuchman and Rapin, 1997). The types of EEG abnormalities have in some cases reported to be similar to

those in the Landau-Kleffner syndrome and in ESES. This is probably only relevant to a minority of children with autism.

Non-convulsive status epilepticus includes a heterogeneous set of states that have in common a change in mental state and EEG evidence of electrographic seizures in the absence of clear convulsive seizures. As these states may be prolonged (at least 30 minutes) and often evade notice because of the subtle nature of the clinical ictal activity, the cognitive effects of non-convulsive status epilepticus are a frequent issue in clinical practice. Often a definite diagnosis of non-convulsive status epilepticus cannot be made until EEG evidence is obtained. Two types of non-convulsive status epilepticus have been distinguished: (1) absence status epilepticus or generalized non-convulsive status epilepticus; and (2) complex partial status epilepticus. Long-term cognitive effects were not observed by some (Scholtes et al., 1995), whereas others (Treiman et al., 1983), found memory impairments persisting over weeks. All studies show a favourable cognitive outcome in the long term. This conclusion is still under debate as animal studies (Lothman et al., 1989) have demonstrated hippocampal neuronal loss in the CA-1 region after inducing a period of non-convulsive status epilepticus in rats. As yet, this discrepancy with human data has not been clarified. However, in only few patients were baseline evaluations available (Dodrill and Wilenski 1990). In the light of this shortcoming, all claims of no cognitive impairment are limited to serious clinical effects, as more subtle effects have not been investigated.

These phenomena are clearly different from TCI. Non-convulsive status is obviously a seizure even if it goes clinically undetected. In the ESES and Landau-Kleffner syndrome prolonged nocturnal discharges cause longer-lasting cognitive and behavioural disturbances. The temporal relation is different: these are not time locked deficits as in TCI even though treatment of discharges may result in an overall improvement of cognition. In addition, a child with ESES or Landau-Kleffner syndrome can also have TCI during daytime interictal discharges independent of the effect of nocturnal discharges. TCI may contribute to the cognitive problems in those patients but this is difficult to examine, not only because most children have too severe deficits to permit formal TCI testing.

If it can be shown that discharges are contributing to a patient's psychosocial difficulties, there arises the question of antiepileptic drug treatment of EEG phenomena. Obviously this proposition has been disputed. However, the point at issue is not whether to treat the EEG, but whether seizures, so subtle as to be recognisable only by EEG and behavioural monitoring, produce disability sufficient to justify treatment. This also questions the terms 'subclinical discharges' and 'interictal discharge': if they are causing cognitive changes like TCI and the behavioural changes as seen in this study, they are strictly speaking not subclinical. Equally, an event associated with disruption of neuropsychological function fulfils the criteria for a seizure and as such is not 'interictal'. The question is whether I should retain the terms 'subclinical epileptiform discharge' or 'interictal discharge' as they are currently used: 'a discharge during which the available methods of clinical observation, applied under particular circumstances, fail to show any changes in the patient' (Aarts et al., 1984) or try and find a new name for this type of epileptiform discharge.

A further dilemma is that discharges seen in the EEG may or may not cause TCI or behavioural problems, depending in which area of the brain they occur. This thesis has confirmed TCI is a specific dysfunction of the brain area where the discharges occur (Aarts et al., 1984) and thus, discharges may cause such a wide range of deficits that they are impractical to assess in every single patient. In addition, for many deficits, particularly behavioural problems, an appropriate test may not exist. Besag suggested the term 'subtle seizure' (Besag, 1994), however, the word seizure suggests at least some change felt by the patient if not a visible manifestation. Patients are in general unaware of EEG discharges and consequent TCI or behavioural changes.

Although one should be open to question ones terminology and thus way of thinking, both terms 'interictal discharges' and 'TCI' have been used in the literature for years and there is good general agreement among the international researchers. Moreover, animal studies have suggested that interictal discharges are indeed different from ictal discharges and the disruption caused has a different electrophysiological explanation. Lebovitz (1979) demonstrated the existence of a prolonged period of inhibition after a single interictal discharge. This has been confirmed in the acute

focal epilepsy animal model by others (for review, see de Curtis and Avanzini, 2001). On the basis of experimental and clinical observations, it has been hypothesized that the interictal discharge-state represents a protective brain mechanism to prevent the occurrence of an ictal discharge(de Curtis and Avanzini, 2001; Librizzi and de Curtis, 2003). Just after an interictal discharge, indeed, hippocampal after-discharges are not effective in generating a subsequent interictal discharge but induce small amplitude potentials subthreshold for the generation of a discharge (Librizzi and de Curtis, 2003). Halgren and colleagues (Halgren et al., 1978 a and b; Halgren and Wilson, 1985) studied the effect of electrical stimulation on behavioural performance during intracranial monitoring in patients with drug-resistant epilepsy. They found evidence that the after-discharges are responsible for disruption of memory function in patients with hippocampal sclerosis. However, such studies are difficult to interpret, since after-discharges may propagate to remote brain regions. These studies suggest interictal discharge-induced synaptic inhibitory after-potentials rather than excessive synchronous electrical discharges of seizure activity may be involved in the disruption of cognitive performance during TCI. Semantic arguments and electrophysiological considerations apart, the case for possible treatment depends on showing that cognitive disturbances accompanying EEG discharges significantly affect the patient's psychosocial functioning in daily life. This study provides evidence to settle the controversy as to whether interictal discharges and TCI cause cognitive impairment (Figure 9.1).

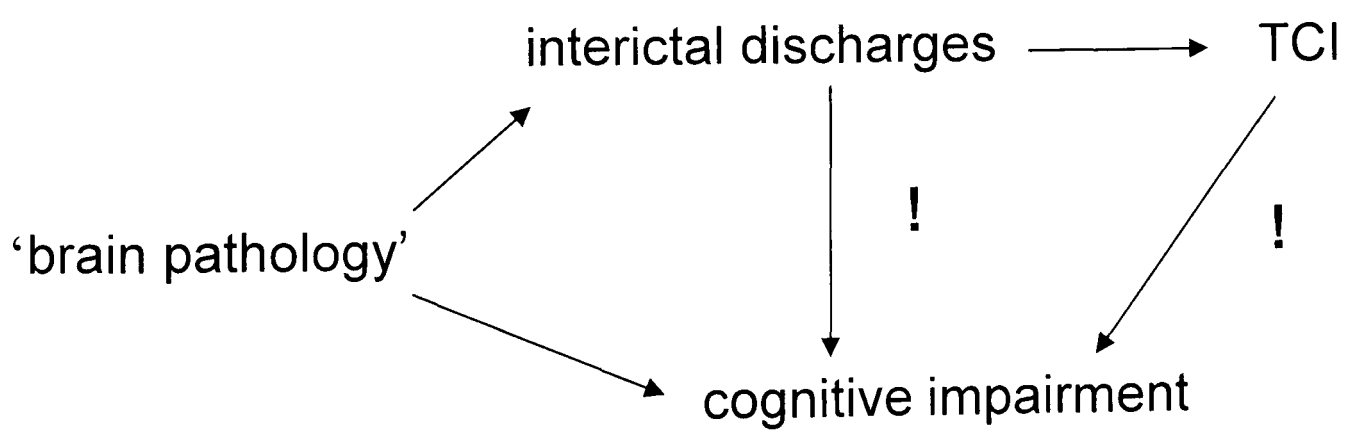


Figure 9.1: Interaction between interictal discharges, brain pathology and cognitive impairment.

Our results have far reaching implications for the treatment of children with epilepsy. Do we under-treat patients with epilepsy by aiming only to suppress clinical seizures? It appears that clinical seizures are only one aspect of neuronal dysfunction in epilepsy. Our study suggests that at least in children with epilepsy and additional behavioural disturbances, treatment of interictal discharges, if present, with appropriate antiepileptic drugs should be considered. Further studies, with larger numbers of patients and long-term follow-up are needed to assess the benefit of treating the EEG in patients with interictal discharges.

9.3. Limitations of the study

The following points have to be considered:

- The patients had a wide range of syndromes, age of onset and different antiepileptic drugs. However, the hypothesis of the study was that interictal discharges are causing TCI and behavioural problems. Thus, regardless of the cause (syndrome), suppression of discharges would improve behaviour and/or cognition.

- Not all patients were completely seizure free. Although the study would have been easier to interpret if all patients were seizure free, this would have made recruitment even more difficult. The rationale behind the inclusion criteria used was, that (1) it is unlikely that few very brief seizures have a relevant impact on behavior and that (2) during a 3-month period (equals one phase) no significant change in seizure frequency would be seen even if some children were not completely seizure free. Patients with so few seizures as to be ordinarily regarded as not requiring a change in medication are no less members of the group of potential candidates for AED treatment to improve behavior than are those who are seizure-free. In the event, the factor 'seizure free' did not influence outcome (see chapter 6, 7 and 8).

- The study was very demanding for children and parents. During the 7-month period they were required to attend at least 5 hospital visits, 4 of which would last 3-4 hours. Furthermore, they had 3 24-hour ambulatory recordings. They had to take medication in addition to their normal antiepileptic drugs although seizures were well-controlled. This resulted in poor compliance in some patients (chapter 5) and withdrawal of consent in 5 patients (nearly 10%).

- Bias in patient selection. All children participating in this study had in addition to epilepsy some degree of behavioural problems or cognitive impairment. Nevertheless, this was not reflected by the baseline behavioral scores. Our results are only applicable for patients with some concern about learning or behavior, which may seem self-evident as one can hardly normalize normal behavior. It would be both unusual and unethical to include in a therapeutic trial subjects not showing the condition that it was proposed to treat. The presence or suspicion of behavioral problems as evidenced by parental complaints was therefore a proper and essential admission criterion. I feel it is appropriate that the population should be 'biased' towards that group of patients to whom the investigation relates.

- Choice of behavioral measure. Although the Conner Rating scale has widely been used to evaluate behavior in children with epilepsy, more recently other tests are used, in particular the Achenbach Child Behavior Checklist. It remains open whether the latter test would have been the better choice.

- Clinical significance of the improvement in behavioral score. It remains unclear what a relatively small improvement in global score means. The Connor Rating scale and other behavioral scales as the Achenbach Child Behavior Checklist have been used in clinical research as a quantitative measure by comparing the t-score before and after intervention rather than using it as a qualitative tool by looking for normal and abnormal scores (Aman et al., 1992; Marston et al., 1993; Weglage et al., 1997). This may provide a statistically significant result which may or may not

be clinically relevant, but this is an inherent problem with all research using behavioral scales in children with mild problems. Since these are the majority of patients seen in epilepsy clinics I feel it is important to study this patient group.

9.4. Further studies

In view of the limitations of the study a further study with more patients, a more effective AED, but fewer investigations would test the results. In particular, the use of the Achenbach Child Behavior Checklist appears advisable. The results of this study make clear that lamotrigine is not very effective in suppressing interictal discharges in the majority of patients. An alternative should be sought. As discussed in section 1.2 few AED are effective in suppressing interictal discharges whilst at the same time having no or few adverse effects on cognition. There is good evidence emerging that levetiracetam has very few cognitive or behavioural side effects, while having good efficacy both in partial and generalised epilepsy (Neyens et al., 1995; Ben-Menachem and Falter, 2000; Cramer et al., 2000). Preliminary studies suggest that it is also effective in suppressing interictal discharges (Gallagher et al., 2004).

In addition to patients with epilepsy there are in particular two groups of patients of great interest:

1. Children with EEG discharges but without clinically evident epilepsy. As discussed in section 1.3 up to 3.5% of school children have interictal discharges, most of whom will have either centro-temporal spikes or generalized 3 per sec spike-and-wave discharges. It has been suggested that these children have an increased risk of behavioral and cognitive problems (Cavazzuti, 1980), but it remains unclear whether suppression of discharges influences psychosocial problems. Until further information is available, treatment of this group of children will continue to a clinical and ethical problem.
2. Children with autistic spectrum disorder with or without epilepsy. Tuchman and Rapin (1997) have suggested an association between seizures and regression in

autistic children. Improvement in behaviour and language in the children after initiation of antiepileptic drug therapy has been seen as evidence that at least important aspects of the behavioural disorders are caused by the epilepsy and may thus be related to the occurrence of epileptiform EEG discharges. Most of this evidence is based on case studies and is not convincing (Nass et al., 1998) and there is inadequate evidence on which to base specific recommendations (Tuchman, 2000). In fact, a recent study on the effects of lamotrigine on autistic behaviour did not show a significant difference to placebo in a group of 28 autistic children aged 3 to 11 years (Belsito et al., 2001). However, no EEG monitoring was performed and consequently data were not separately analysed for patients with and without interictal discharges. Autistic children have not been investigated for TCI and the exact effect of discharges in the autistic spectrum disorder is unclear. Further studies should include this group of children, whose behavioural problems are often severe and their treatment options limited.

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